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Thomas JG Chambers
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20

Endocrinology

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Clinical examination in endocrine disease

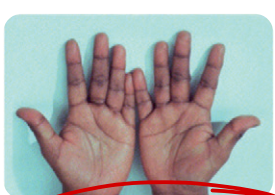
5 Blood pressure
Hypertension (a/gh)
Hypotension (a)
Orthostatic hypotension (a)

4 Pulse
Tachycardic (t)
Bradycardic (t)
Irregularly irregular (t)

3 Skin
Hirsutism (a/g)
Dry/greasy (t)
Pigmentation (a)
Bruising (a)
Vitiligo
Striae (a)
Coarse (gh)

Vitiligo in organ-specific autoimmune disease

2 Hands
Palmar erythema (t)
Tremor (t)
Spade like/doughy consistency (gh)
Carpal tunnel syndrome (gh)
Pigmentation of creases (a)

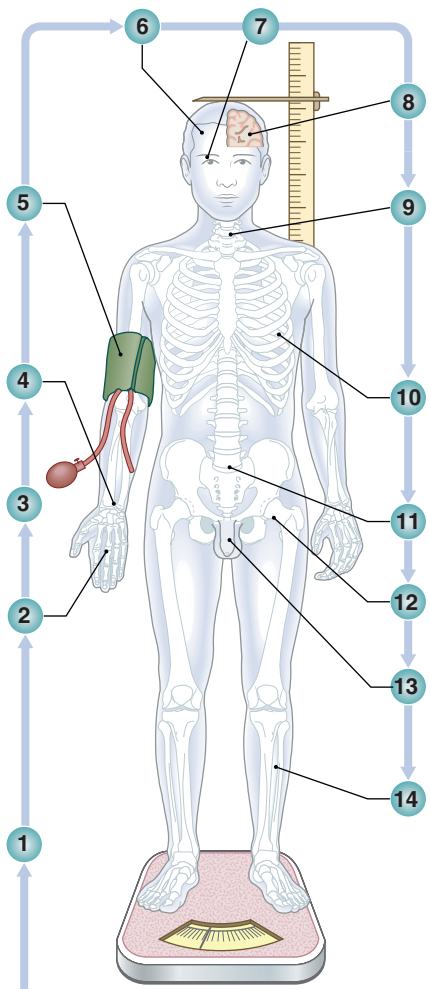


Pigmentation of creases due to high ACTH levels in Addison disease

Acromegalic hands. Note soft tissue enlargement causing 'spade-like' changes

1 Height and weight
Increased weight (a/t)
Reduced weight (t)

6 Head
Alopecia (t)
Hirsutism (a/g)
Prognathism (gh)
Mooning (a)
Frontal bossing (gh)
Complexion (t)



Observation
- Most clinical signs in endocrinology can be detected by observation alone
- Examination may focus on the syndrome of features associated with the gland or hormone of concern

7 Eyes
Graves ophthalmopathy (t) (see opposite)
Bitemporal hemianopia (p)

8 Brain
Psychosis (a/t)
Depression (a/t)

9 Neck
Hoarse voice (t)
Virilised (g)
Goitre (t) (see opposite)
Thyroid nodules (t)

Multinodular goitre

10 Breasts
Galactorrhoea (p)
Gynaecomastia (g/a/p)

11 Habitus
Central obesity (a)

12 Bones
Kyphosis (a/ca)

13 Genitalia
Virilisation (g)
Testicular volume (g)
Pubertal development (g)

14 Legs
Proximal myopathy (a/t)
Myxoedema (t)

Pretibial myxoedema in Graves disease

Disorder of:
(a) = hypothalamus–pituitary–adrenal axis
(ca) = calcium
(g) = hypothalamus–pituitary–gonad axis
(gh) = growth hormone
(p) = pituitary
(t) = hypothalamus–pituitary–thyroid axis

Insets: (Acromegalic hands) From Baynes JW, Dominiczak MH. Medical biochemistry. 4th ed. Saunders; 2014. (Pigmentation of creases) From Shifrin AL. Endocrine emergencies. Elsevier; 2022. (Vitiligo) From Ferri FF. Ferri's fast facts in dermatology: A practical guide to skin disease and disorders. 2nd ed. Saunders; 2019. (Goitre) From Mosby's dictionary of medicine, nursing & health professions. 4th ed. Mosby; 2025. (Myxoedema) From Gawkrodger D, Ardern-Jones MR. Dermatology. 8th ed. Elsevier; 2025.

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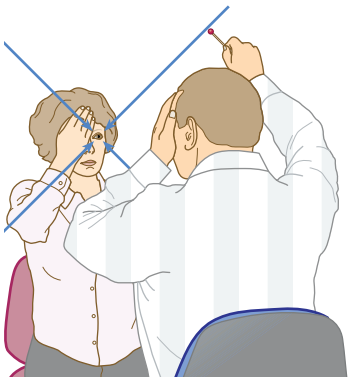
7 Examination of the visual fields by confrontation



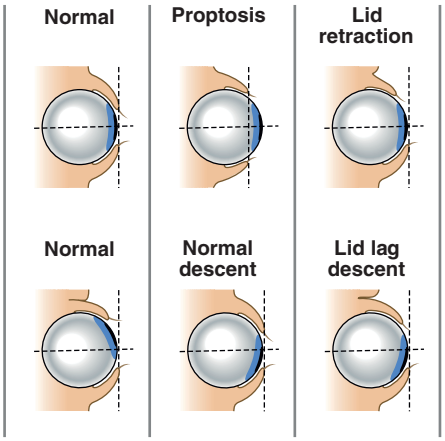
- Sit opposite patient
- You and patient cover opposite eyes
- Bring red pin (or wiggling finger) slowly into view from extreme of your vision, as shown
- Ask patient to say 'now' when it comes into view
- Continue to move pin into centre of vision and ask patient to tell you if it disappears
- Repeat in each of four quadrants
- Repeat in other eye

A bitemporal hemianopia is the classical finding in pituitary macroadenomas (p. 736)

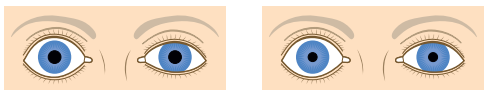
7 Examination in Graves ophthalmopathy

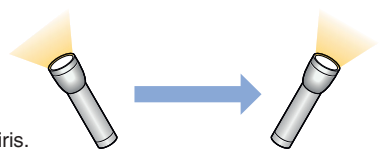
- **Inspect** from front and side
  - Periorbital oedema (Fig. 20.8)
  - Conjunctival inflammation (chemosis)
  - Corneal ulceration
  - Proptosis (exophthalmos)*
  - Lid retraction*
- **Range of eye movements**
  - Lid lag on descending gaze*
  - Diplopia on lateral gaze
- **Pupillary reflexes**
  - Relative afferent defect (pupils constrict further on swinging light to unaffected eye, Box 27.21)
- **Vision**
  - Visual acuity impaired
  - Loss of colour vision
  - Visual field defects
- **Ophthalmoscopy**
  - Optic disc pallor
  - Papilloedema

*Note position of eyelids relative to iris.



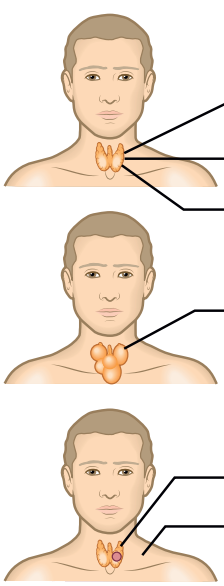
Right proptosis and afferent pupillary defect





9 Examination of the thyroid gland

- **Inspect** from front to side
- **Palpate** from behind
  - Thyroid moves on swallowing
  - Check if lower margin is palpable
  - Cervical lymph nodes
  - Tracheal deviation
- **Auscultate** for bruit
  - Ask patient to hold breath
  - If present, check for radiating murmur
- **Percuss** for retrosternal thyroid
- Consider systemic signs of thyroid dysfunction (Box 20.7) incl. tremor, palmar erythema, warm peripheries, tachycardia, lid lag
- Consider signs of Graves disease incl. ophthalmopathy, pretibial myxoedema
- Check for Pemberton sign, i.e. facial engorgement when arms raised above head



Abnormal findings

- Diffuse soft goitre with bruit
  - Graves disease (p. 702)
- Diffuse firm goitre
  - Hashimoto thyroiditis (p. 705)
- Diffuse tender goitre
  - Subacute thyroiditis (p. 705)
- Multinodular goitre (p. 706)
  - ± Retrosternal extension, tracheal compression
- Solitary nodule (p. 701)
  - Adenoma, cyst or carcinoma
- Cervical lymphadenopathy
  - Suggests carcinoma

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Hormones are chemical messengers critical for maintaining homeostasis, regulating responses to environmental challenges, controlling growth and reproduction. Endocrinology concerns the synthesis, secretion and action of hormones. Endocrine disease may result directly from pathology within endocrine glands, and indirectly from disrupted hormone signalling. This chapter describes the principles of endocrinology before discussing the physiology and pathology of each gland in turn.

An overview of endocrinology

Functional anatomy and physiology

Most endocrine glands are controlled by hormones released from the anterior pituitary gland, although some, such as the parathyroid glands and pancreas, respond directly to metabolic signals. Hormone secretion from the anterior pituitary is controlled in turn by messengers produced in the hypothalamus and released into the hypothalamo-hypophyseal portal system, which drains directly down the pituitary stalk (Fig. 20.1). Posterior pituitary hormones are synthesised in the hypothalamus and transported down nerve axons, to be released from the posterior pituitary. Hormone release in the hypothalamus and pituitary is regulated by numerous neuropeptides and by feedback control by hormones produced by the target glands (thyroid, adrenal cortex and gonads). These integrated endocrine systems are called 'axes' and are listed in Figure 20.2.

A wide variety of molecules can act as hormones. Small peptides such as insulin, glycoproteins such as thyroid-stimulating hormone, and amines such as noradrenaline (norepinephrine) bind to specific receptors on the membrane of their target cells. Activation of these receptors triggers a cascade of intracellular signalling to affect cell function. Steroid (for example cortisol) and thyroid hormones cross the cell membrane and exert their effects predominantly by binding to intracellular receptors forming complexes that affect the transcriptional activity of target genes.

The classical model of endocrine function involves hormones synthesised in endocrine glands, which are released into the circulation and act at distal sites (as in Fig. 20.1). Hormone activity is also regulated by a number of 'fine-tuning' physiological processes: (1) hormones may be activated or deactivated locally at their target organ (local deiodinases activate and deactivate thyroid hormones); (2) circulating peptide hormones, such as insulin, have a short half-life due to degradation by peptidases thereby limiting the risk of hormone activity when it is no longer required; (3) hormones may be rendered inactive by binding to large proteins circulating in the bloodstream, leaving a small pool of circulating active 'free' hormone (thyroid hormone is almost entirely bound to carrier proteins). Some hormones can act in a paracrine fashion

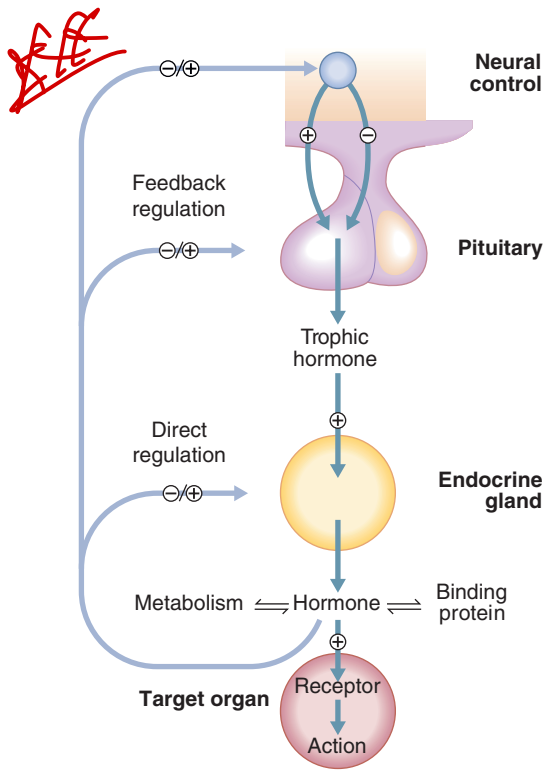

Fig. 20.1 An archetypal endocrine axis. Regulation by negative feedback and direct control is shown, along with the equilibrium between active circulating free hormone and bound or metabolised hormone.

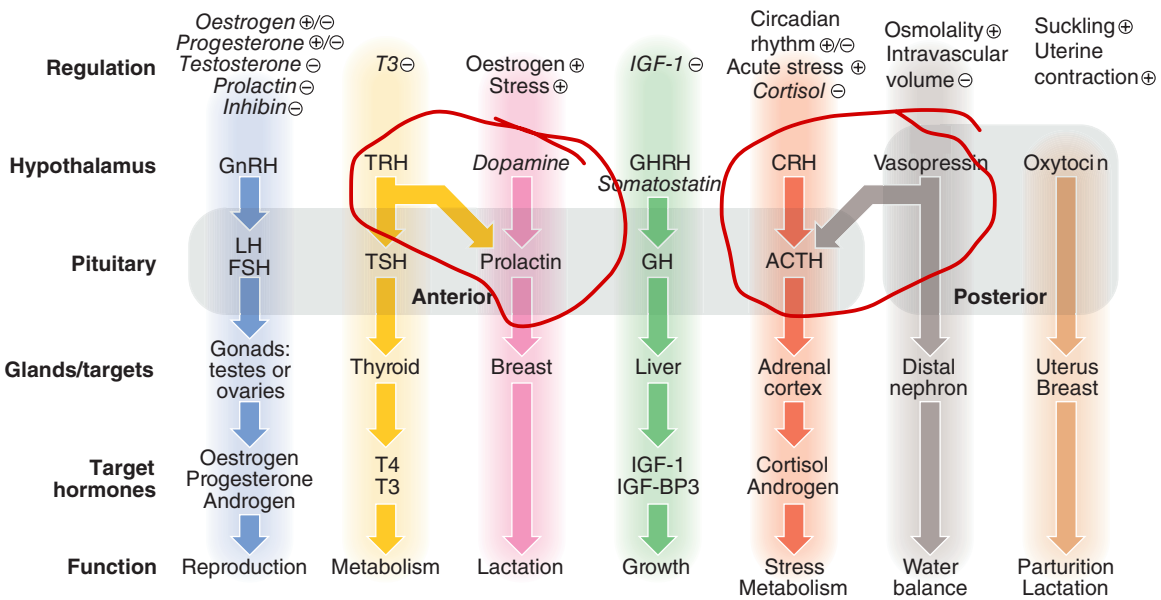

Fig. 20.2 The principal endocrine 'axes'. Some major endocrine glands are not controlled by the pituitary. These include the parathyroid glands (regulated by calcium concentrations, p. 717), the adrenal zona glomerulosa (regulated by the renin–angiotensin system, p. 721) and the endocrine pancreas (p. 733). Italics show negative regulation. (ACTH = adrenocorticotrophic hormone; CRH = corticotrophin-releasing hormone; FSH = follicle-stimulating hormone; GH = growth hormone; GHRH = growth hormone-releasing hormone; GnRH = gonadotrophin-releasing hormone; IGF-1 = insulin-like growth factor-1; IGF-BP3 = IGF-binding protein-3; LH = luteinising hormone; T3 = triiodothyronine; T4 = thyroxine; TRH = thyrotrophin-releasing hormone; TSH = thyroid-stimulating hormone; vasopressin = antidiuretic hormone (ADH))

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to affect adjacent cells, or act in an autocrine way to affect behaviour of the cell that produced the hormone.

Endocrine pathology

For each endocrine axis or major gland, diseases can be classified as shown in Box 20.1. Pathology arising within the gland is often called 'primary' disease (e.g. primary hypothyroidism resulting from Hashimoto thyroiditis), while abnormal stimulation of the gland is often called 'secondary' disease (e.g. secondary hypothyroidism due to thyroid-stimulating hormone deficiency in patients with pituitary tumours). Some pathological processes can affect multiple endocrine glands; these may have a genetic basis (such as the multiple endocrine neoplasia (MEN) syndromes) or be a consequence of therapy for another disease (such as following systemic anti-cancer treatment and/or radiotherapy).

Investigation of endocrine disease

As chemical messengers, most hormones can be measured in samples of bodily fluids, commonly in blood, urine and saliva. Physiological hormone secretion can be highly variable and thus the timing and context of a sample may impact significantly on the interpretation of results; for example, a low cortisol value may be normal at 2300 hrs, but indicate adrenal insufficiency if assessed at 0800 hrs. Furthermore, some hormones are labile and have specific requirements for sample processing (for example, collection into particular tubes, transport on ice, rapid processing). Local protocols for hormone measurement should be followed carefully.

For some hormones, dynamic tests may be required to identify disrupted secretion; suppression tests are used to assess for hypersecretion (for example, dexamethasone suppression testing for excessive cortisol secretion); and stimulation tests are required where there is concern about insufficiency (for example, ACTH stimulation testing [also known as short Synacthen, corticotrophin, cosyntropin or tetracosactide stimulation test] for adrenal insufficiency). The choice of stimulus can help to determine the level of the endocrine axis affected; whilst the ACTH stimulation test will assess primarily adrenal responsiveness, an insulin tolerance test (inducing hypoglycaemia) will assess appropriate hypothalamus, pituitary and adrenal response to stress. Intra- and inter-individual variation in hormone levels means that some tests may have poor sensitivity and specificity; an understanding of the accuracy of the test being interpreted is thus important.

The context in which a hormone has been measured will affect its concentration, with important implications for interpretation of results. For example, parathyroid hormone levels may be reported within the reference range for a patient with hypercalcaemia; in this context one would expect suppressed parathyroid hormone (PTH) levels; thus, levels are 'inappropriately normal' and suggestive of hyperparathyroidism. The principles of investigation are shown in Box 20.2. The choice of test is often pragmatic, taking local access to reliable sampling facilities and laboratory measurements into account.

20.1 Classification of endocrine disease

Hormone excess
- Primary gland hypersecretion
- Secondary to excess gland stimulation

Hormone deficiency
- Primary gland failure
- Secondary to deficient trophic hormone

Hormone hypersensitivity
- Failure of inactivation of hormone
- Target organ over-activity/hypersensitivity

Hormone resistance
- Failure of activation by hormone
- Target organ resistance

Non-functioning tumours
- Benign
- Malignant

Presenting problems in endocrine disease

Endocrine diseases present in many ways to clinicians in different disciplines. The classical syndromes associated with disorders of individual glands are described in the following sections. However, patients often present with non-specific symptoms (Box 20.3) or are seemingly asymptomatic with only biochemical abnormalities. Endocrine diseases are also encountered within the differential diagnosis of common presentations discussed in other chapters of this book, including electrolyte

20.2 Principles of endocrine investigation

Timing of measurement
- Release of many hormones is rhythmical (pulsatile, circadian or monthly), random measurement may be invalid and specifically timed, sequential or dynamic tests may be required

Choice of dynamic biochemical test
- If hormone deficiency is suspected, choose a stimulation test
- If hormone excess is suspected, choose a suppression test
- The more tests there are to choose from, the less likely it is that any single test is infallible, so avoid interpreting one result in isolation

Imaging
- 'Functional' as well as conventional 'structural' imaging can be performed as secretory endocrine cells often take up labelled substrates, e.g. radio-labelled iodine or octreotide
- Most endocrine glands have a high prevalence of 'incidentalomas', so do not scan unless the biochemistry confirms endocrine dysfunction or the primary problem is a tumour

Biopsy
- Many endocrine tumours are difficult to classify histologically (e.g. adrenal carcinoma and adenoma)

20.3 Examples of non-specific presentations of endocrine disease

Symptom	Most likely endocrine disorder(s)
Lethargy and depression	Hypothyroidism, diabetes mellitus, hyperparathyroidism, hypogonadism, adrenal insufficiency, Cushing syndrome
Weight gain	Hypothyroidism, Cushing syndrome
Weight loss	Thyrotoxicosis, adrenal insufficiency, diabetes mellitus
Polyuria and polydipsia	Diabetes mellitus, arginine vasopressin resistance or insufficiency, hyperparathyroidism, hypokalaemia (Conn syndrome)
Heat intolerance*	Thyrotoxicosis
Palpitation	Thyrotoxicosis, phaeochromocytoma
Headache	Acromegaly, pituitary tumour, phaeochromocytoma
Muscle weakness (usually proximal)	Thyrotoxicosis, Cushing syndrome, hypokalaemia (e.g. Conn syndrome), hyperparathyroidism, hypogonadism
Coarsening of features	Acromegaly, hypothyroidism
Sweating*	Thyrotoxicosis, hypogonadism, hypoglycaemia, carcinoid syndrome, phaeochromocytoma

*Heat intolerance and sweating are common features of menopause.

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abnormalities (Ch. 19), hypertension (Ch. 16), obesity (Ch. 5) and osteoporosis (Ch. 25). The non-specific presentation of some endocrine disorders means diagnosis relies on astute clinical observation and so it is important to be familiar with their key features.

The thyroid gland

Thyroid disease has an incidence of 2.6 cases per 1000 per year in European populations with the rate 5 times higher in females than males. The incidence is twice as high in populations deficient in iodine. Diseases of the thyroid are summarised in Box 20.4. Thyroid hormones regulate cellular differentiation and metabolism in virtually all nucleated cells, meaning disorders of thyroid function have diverse manifestations. Structural disease of the thyroid gland, such as goitre or thyroid nodules, may not necessarily affect thyroid function.

Functional anatomy, physiology and investigations

Thyroid physiology is illustrated in Figure 20.3. Parafollicular C cells secrete calcitonin, which reduces plasma calcium but is seemingly redundant in humans. Follicular cells synthesise thyroid hormones; they secrete thyroglobulin (Tg), a scaffold protein, and transport iodide into the thyroid colloid. Here, thyroid peroxidase catalyses the iodination of tyrosine residues, forming triiodothyronine (T3) and the prohormone thyroxine (T4). Iodide is essential for thyroid hormone synthesis.

The thyroid secretes predominantly T4 and a small amount of T3; approximately 85% of T3 is produced peripherally from T4 by deiodinase enzymes that regulate localised thyroid hormone activity. T4 has a much longer half-life in blood than T3 (approximately 1 week compared with approximately 18 hours).

T3 and T4 circulate in plasma almost entirely (>99%) protein-bound, predominantly to thyroxine-binding globulin (TBG) but also to albumin and transthyretin. Only unbound or free hormones are transported into cells to activate the thyroid receptor. Historically, laboratories used assays that measured total T4 and T3; however, it is now common to measure free T4 and free T3. The advantage of free hormone measurements is that they are not influenced by changes in the concentration of binding proteins. For example, TBG levels are increased by oestrogen (such as in the combined oral contraceptive pill), which results in raised total T3 and T4, whilst free thyroid hormone levels remain normal.

Production of T3 and T4 in the thyroid gland is stimulated by thyroid-stimulating hormone (TSH). TSH is a glycoprotein released from the thyrotroph cells of the anterior pituitary primarily in response to the hypothalamic tripeptide, thyrotrophin-releasing hormone (TRH). A circadian rhythm of TSH secretion can be demonstrated with a peak at about midnight and trough in the afternoon. However, variation in TSH (and free T3) secretion is modest, meaning thyroid function can be assessed reliably from blood drawn at any time of day.

T3 inhibits TRH and TSH production in the hypothalamus and pituitary; when plasma concentrations of T3 and T4 are raised in patients with thyrotoxicosis, TSH secretion should be suppressed. Conversely, in hypothyroidism due to thyroid gland dysfunction, low T3 and T4 should be associated with high circulating TSH levels. The relationship between TSH and T4 is classically described as inverse log-linear (Fig. 20.4), such that small changes in TSH levels reciprocate larger changes in free T4. For this reason, TSH is usually regarded as the most useful investigation of thyroid function, especially in the context of assessing replacement.

Discrepant thyroid function tests, where TSH and thyroid hormones do not reciprocate as expected, most commonly occur due to problems with hormone measurement, but may indicate less common pathology. For example, in patients with pituitary disease, TSH may be inappropriately low or 'normal' in the context of low free T4 levels (see Box 20.5 and Box 20.51). Further, there can be a lag of several weeks in the thyrotroph response to changes to thyroid hormone levels; for example, levothyroxine therapy will raise T4 and T3 levels within approximately 2 weeks, but it can take 4–6 weeks for the TSH to reach a steady state. Heterophilic antibodies (host antibodies with affinity to the animal antibodies used in immunoassays) can interfere with the TSH assay and cause a spurious high or low measurement. Common patterns of abnormal thyroid function test results and their interpretation are shown in Box 20.5.

Other investigations of thyroid disease include the measurement of antibodies targeting the TSH receptor (TRAb) or other thyroid antigens (see Box 20.8), radioisotope imaging, fine needle aspiration biopsy and ultrasound. Their use is described below.

i 20.4 Classification of thyroid disease

	Primary	Secondary
Hormone excess	Graves disease Multinodular goitre Adenoma Subacute thyroiditis	TSHoma
Hormone deficiency	Hashimoto thyroiditis Atrophic hypothyroidism	Hypopituitarism
Hormone hypersensitivity	–	
Hormone resistance	Thyroid hormone resistance syndrome 5′-monodeiodinase deficiency	
Non-functioning tumours	Differentiated carcinoma Medullary carcinoma Lymphoma	

Presenting problems in thyroid disease

The most common presentations are hyperthyroidism (thyrotoxicosis), hypothyroidism and enlargement of the thyroid (goitre or thyroid nodule). Increasingly, thyroid dysfunction is identified in patients who are asymptomatic or who have relatively non-specific symptoms such as fatigue or changes to weight.

Thyrotoxicosis

Thyrotoxicosis describes a state in which the patient exhibits clinical features arising from elevated circulating levels of thyroid hormone. The most common causes are Graves disease, multinodular goitre, autonomously functioning thyroid nodules (toxic adenoma) and thyroiditis (Box 20.6).

Clinical assessment

The clinical manifestations of thyrotoxicosis are shown in Box 20.7, and an approach to differential diagnosis is given in Figure 20.5. The most common symptoms are weight loss with a normal or increased appetite (although around 5% patients may exhibit weight gain), heat intolerance, palpitations, tremor and irritability. Tachycardia, palmar erythema and lid lag are common clinical signs. Not all patients have a palpable goitre, but experienced clinicians may discriminate the diffuse soft goitre of Graves disease from the irregular enlargement of a multinodular goitre. All causes of thyrotoxicosis can cause lid retraction and lid lag, due to potentiation of sympathetic innervation of the levator palpebrae muscles, but only Graves disease causes other features of ophthalmopathy, including periorbital oedema, conjunctival irritation, exophthalmos and diplopia. Pretibial myxoedema and the rare thyroid acropachy (a periosteal hypertrophy, indistinguishable from finger clubbing) are also specific to Graves disease (see p. 690).

Investigations

The first-line investigations are serum free T4 and TSH. If abnormal values are found, the tests should be repeated and the abnormality confirmed in view of the likely need for prolonged medical treatment or destructive

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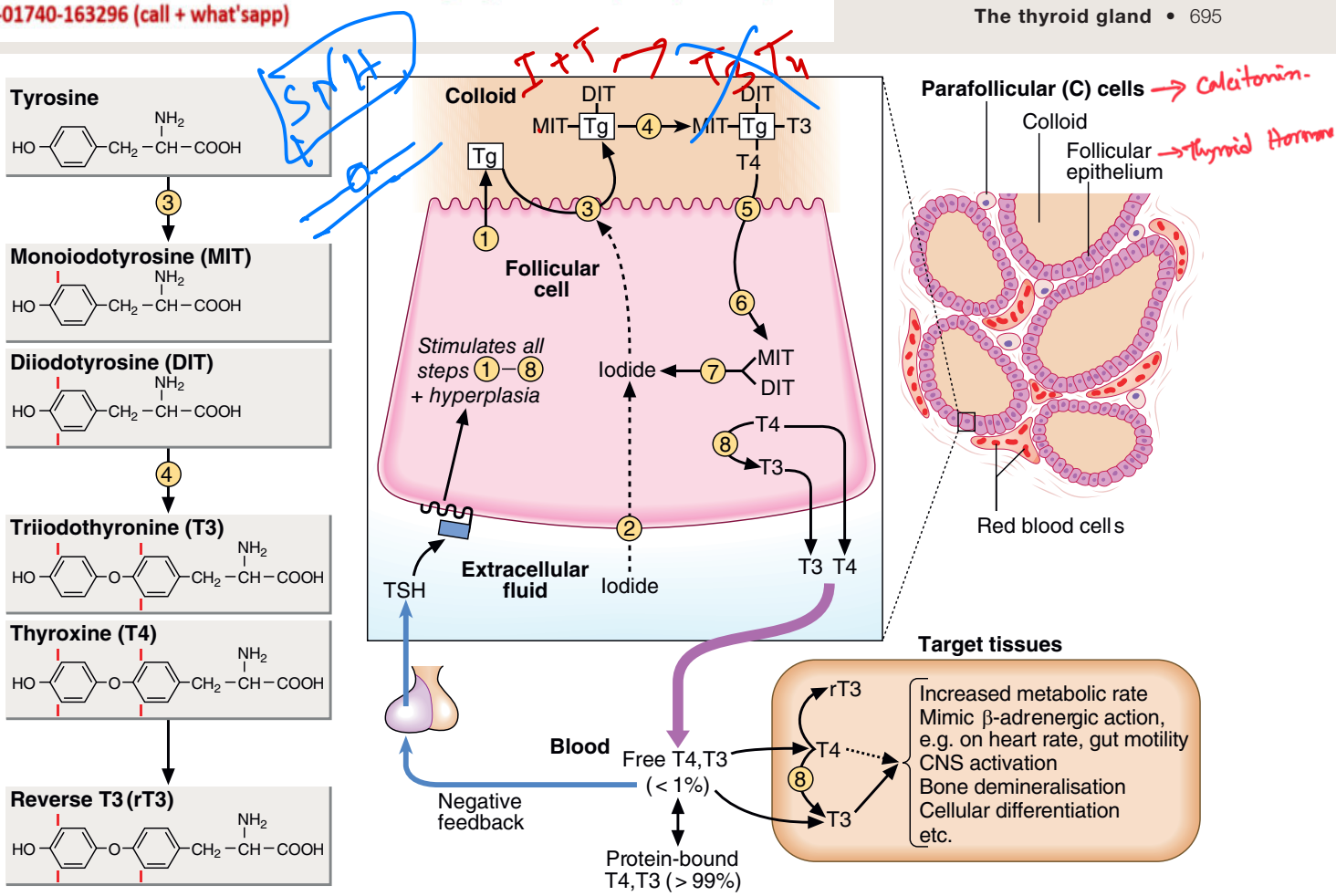

Fig. 20.3 Structure and function of the thyroid gland. (1) Thyroglobulin (Tg) is synthesised and secreted into the colloid of the follicle. (2) Inorganic iodide (I^-) is actively transported into the follicular cell ('trapping'). (3) Iodide is transported on to the colloidal surface by a transporter (pendrin, defective in Pendred syndrome, p. 709) and 'organified' by the thyroid peroxidase enzyme, which incorporates it into the amino acid tyrosine on the surface of Tg to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). (4) Iodinated tyrosines couple to form triiodothyronine (T3) and thyroxine (T4). (5) Tg is endocytosed. (6) Tg is cleaved by proteolysis to free the iodinated tyrosine and thyroid hormones. (7) Iodinated tyrosine is dehalogenated to recycle the iodide. (8) T4 is converted to T3 by 5′-monodeiodinase. (CNS = central nervous system; TSH = thyroid-stimulating hormone)

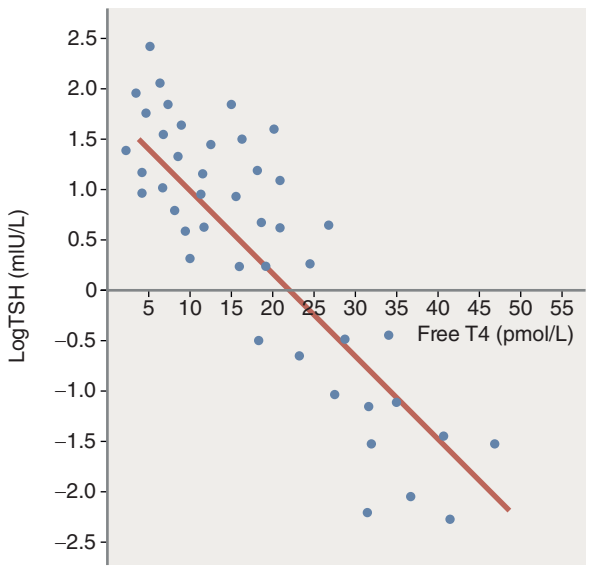

Fig. 20.4 The relationship between serum thyroid-stimulating hormone (TSH) and free T4. Due to the classic negative feedback loop between T4 and TSH, there is an inverse relationship between serum free T4 and the log of serum TSH. To convert pmol/L to ng/dL, divide by 12.87.

therapy. In most patients, serum T3 and T4 are both elevated; elevation of only T3 (T3 toxicosis) is seen in about 5% of presentations. Therefore, free T3 should be assessed in cases with suppressed TSH and normal free T4 levels (T4 usually being at the upper end of the reference range). Serum TSH is undetectable in primary thyrotoxicosis, but values can be raised (or inappropriately normal) in the extremely rare syndrome of secondary thyrotoxicosis caused by a TSH-producing pituitary adenoma, or where uncommon mutations in the thyroid hormone receptor cause thyroid hormone resistance. When biochemical thyrotoxicosis has been confirmed, measurement of TSH receptor antibodies (TRAb, elevated in Graves disease; Box 20.8) is recommended. Where TRAb assessment is not available, or is not detected, radioisotope scanning may help with diagnosis, as shown in Figure 20.5. Other non-specific laboratory abnormalities are common (Box 20.9). An electrocardiogram (ECG) may demonstrate sinus tachycardia and around 5%–10% patients may have atrial fibrillation.

Radio-iodine uptake tests measure the proportion of isotope that is trapped in the whole gland, but have been largely superseded by technetium-99m (^{99m}Tc) scintigraphy scans, which are quicker to perform with a lower dose of radioactivity and provide a higher-resolution image. In low-uptake thyrotoxicosis, the cause is usually a transient thyroiditis; an increase in global uptake is consistent with Graves disease, whilst localised uptake may be demonstrated in toxic nodular disease.

Occasionally, patients induce 'factitious thyrotoxicosis' by consuming excessive amounts of a thyroid hormone preparation, most often

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20.5 How to interpret thyroid function test results

TSH	T4	T3	Most likely interpretation(s)
Undetectable	Raised	Raised	Primary thyrotoxicosis
Undetectable or low	Raised	Normal	Over-treatment of hypothyroidism with levothyroxine Factitious thyrotoxicosis
Undetectable	Normal[1]	Raised	Primary T3 toxicosis
Undetectable	Normal[1]	Normal[1]	Subclinical thyrotoxicosis
Undetectable or low	Raised	Low or normal	Non-thyroidal illness Amiodarone therapy
Undetectable or low	Low	Raised	Over-treatment of hypothyroidism with liothyronine (T3)
Undetectable	Low	Low	Secondary hypothyroidism[4] Transient thyroiditis in evolution
Normal	Low	Low[2]	Secondary hypothyroidism[4]
Mildly elevated 5–20 mIU/L	Low	Low[2]	Primary hypothyroidism Secondary hypothyroidism[4]
Elevated > 20 mIU/L	Low	Low[2]	Primary hypothyroidism
Mildly elevated 5–20 mIU/L	Normal[3]	Normal[2]	Subclinical hypothyroidism
Elevated 20–500 mIU/L	Normal	Normal	Artefact Heterophilic antibodies (host antibodies with affinity to the animal antibodies used in TSH assays)
Elevated	Raised	Raised	Non-adherence to levothyroxine replacement – recent 'loading' dose Secondary thyrotoxicosis[4] Thyroid hormone resistance

[1]Usually upper part of reference range.
[2]T3 is not a sensitive indicator of hypothyroidism and should not be requested.
[3]Usually lower part of reference range.
[4]i.e. Secondary to pituitary or hypothalamic disease. Note that TSH assays may report detectable TSH.
(TSH = thyroid-stimulating hormone)

20.6 Causes of thyrotoxicosis and their relative frequencies

Cause	Frequency[1] (%)
Graves disease	76
Multinodular goitre	14
Solitary thyroid adenoma	5
Thyroiditis	
Subacute (de Quervain)[2]	3
Post-partum[2]	0.5
Iodide-induced	
Drugs (amiodarone)[2]	1
Radiographic contrast media[2]	–
Iodine supplementation programme[2]	–
Extrathyroidal source of thyroid hormone	
Factitious thyrotoxicosis[2]	0.2
Struma ovarii[2,3]	–
TSH-induced	
TSH-secreting pituitary adenoma	0.2
Choriocarcinoma and hydatidiform mole[4]	–
Follicular carcinoma ± metastases	0.1

[1]In a series of 2087 patients presenting to the Royal Infirmary of Edinburgh over a 10-year period.
[2]Characterised by negligible radioisotope uptake.
[3]i.e. Ovarian teratoma containing thyroid tissue.
[4]Human chorionic gonadotrophin has thyroid-stimulating activity.
(TSH = thyroid-stimulating hormone)

levothyroxine. Exogenous levothyroxine suppresses pituitary TSH secretion and thus thyroid activity. Thyroglobulin production and release of endogenous thyroid hormones are reduced. The T4:T3 ratio (typically 30:1 in conventional thyrotoxicosis) is increased to above 70:1 because circulating T3 in factitious thyrotoxicosis is derived exclusively from the peripheral deiodination of T4. The combination of negligible iodine uptake, high T4:T3 ratio and a low or undetectable thyroglobulin is diagnostic.

Management

Definitive treatment of thyrotoxicosis depends on the underlying cause and may include antithyroid drugs, radioactive iodine or surgery. A non-selective β-adrenoceptor antagonist (β-blocker), such as propranolol (80–160 mg in 4 divided doses), will alleviate but not abolish symptoms in most patients within 24–48 hours. Beta-blockers should not be used for long-term treatment of thyrotoxicosis, but are invaluable in the short term while patients are awaiting diagnosis and treatment. Verapamil may be used as an alternative to β-blockers, e.g. in patients with asthma, but usually is only effective in improving tachycardia and is less helpful managing other systemic symptoms of thyrotoxicosis.

Atrial fibrillation in thyrotoxicosis

Atrial fibrillation occurs in about 5%–10% of patients with thyrotoxicosis. The incidence is higher in men and increases with age, such that almost half of all males with thyrotoxicosis over the age of 60 are affected. Moreover, subclinical thyrotoxicosis (see p. 701) is a risk factor for atrial fibrillation. Characteristically, the ventricular rate is little influenced by digoxin (likely due to increased clearance) but responds to the addition of a β-blocker. Thromboembolic vascular complications are particularly common in thyrotoxic atrial fibrillation, so anticoagulation is required unless contraindicated. Once thyroid hormone and TSH concentrations have returned to normal, atrial fibrillation will spontaneously revert to sinus rhythm in about 50% of patients; cardioversion should be considered in the remainder.

Thyrotoxic crisis ('thyroid storm')

This is a rare but life-threatening complication of thyrotoxicosis with mortality rates of 8%–25%. The most prominent signs are fever, agitation, delirium, tachycardia or atrial fibrillation and, in the older patient, cardiac failure. Thyrotoxic crisis is a medical emergency. It is precipitated most commonly

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20.7 Clinical features of thyroid dysfunction

Thyrotoxicosis		Hypothyroidism	
Symptoms	**Signs**	**Symptoms**	**Signs**
Common			
Weight loss despite normal or increased appetite	Weight loss	Weight gain	Weight gain
Heat intolerance, sweating	Tremor	Cold intolerance	
Palpitations, tremor	Palmar erythema	Fatigue, somnolence	
Dyspnoea, fatigue	Sinus tachycardia	Dry skin	
Irritability, emotional lability	Lid retraction, lid lag	Dry hair	
		Menorrhagia	
Less common			
Osteoporosis (fracture, loss of height)	Goitre with bruit[1]	Constipation	Hoarse voice
Diarrhoea, steatorrhoea	Atrial fibrillation[2]	Hoarseness	Facial features:
Angina	Systolic hypertension/	Carpal tunnel syndrome	Purplish lips
Ankle swelling	increased pulse pressure	Alopecia	Malar flush
Anxiety, psychosis	Cardiac failure[2]	Aches and pains	Periorbital oedema
Muscle weakness	Hyper-reflexia	Muscle stiffness	Loss of lateral eyebrows
Periodic paralysis (predominantly in Chinese and	Ill-sustained clonus	Deafness	Anaemia
other Asian groups)	Proximal myopathy	Depression	Carotenaemia
Pruritus, alopecia	Bulbar myopathy[2]	Infertility	Erythema ab igne
Amenorrhoea/oligomenorrhoea			Bradycardia, hypertension
Infertility, spontaneous abortion			Delayed relaxation of reflexes
Loss of libido, impotence			Dermal myxoedema
Excessive lacrimation			
Rare			
Vomiting	Gynaecomastia	Psychosis (myxoedema madness)	Ileus, ascites
Apathy	Spider naevi	Galactorrhoea	Pericardial and pleural effusions
Anorexia	Onycholysis	Impotence	Cerebellar ataxia
Exacerbation of asthma	Pigmentation		Myotonia

[1]In Graves disease only.
[2]Features found particularly in older patients.

by infection in a patient with unrecognised or inadequately treated thyrotoxicosis. It may also develop in patients with uncontrolled thyrotoxicosis shortly after thyroid manipulation during thyroidectomy or within a few days of iodine-131 (^{131}I) therapy, when acute radiation damage may lead to a transient rise in serum thyroid hormone levels. Urgent specialist endocrine input should be sought in cases of suspected 'thyroid storm', both to confirm the diagnosis and provide advice on appropriate treatment.

Patients should be rehydrated. Beta-blockade using propranolol, either orally (40–80 mg 4 times daily) or intravenously (0.5–2 mg, slow bolus) should be initiated; close monitoring may be needed for patients with congestive heart failure. Oral propylthiouracil (PTU) (200–250 mg every 4 hours) should be given to inhibit the synthesis of new thyroid hormone. PTU is preferred to carbimazole (20 mg every 6 hours) as it also inhibits the conversion of T4 to T3. PTU and propranolol can be administered by nasogastric tube if necessary; however, IV treatment may be necessary due to reduced gastrointestinal absorption. Both glucocorticoids (hydrocortisone 100 mg IV every 8 hours) and iodine reduce the conversion of T4 to active T3. Iodine (saturated potassium iodide solution/Lugol's solution) 0.25 mL every 6 hours orally or sodium ipodate, a radiographic contrast medium (500 mg per day orally), should restore serum T3 levels to normal in 48–72 hours. Administration 1 hour after PTU or carbimazole should limit the risk of stimulating thyroid hormone release (p. 706). After 10–14 days the patient can usually be maintained on carbimazole alone.

Hyperthyroidism in old age

Some of the diagnostic and management challenges of hyperthyroidism in older people are highlighted in Box 20.12.

Hypothyroidism

Hypothyroidism has a prevalence of 0.5%–5% in populations replete in iodine and may approach 10% in populations with endemic iodine deficiency. Autoimmune disease (Hashimoto thyroiditis), thyroid failure following ^{131}I or surgical treatment of thyrotoxicosis account for over 90% of cases, except in areas where iodine deficiency is endemic (Box 20.10). Women are affected approximately six times more frequently than men.

Clinical assessment

The clinical presentation depends on the duration and severity of the hypothyroidism. Those in whom complete thyroid failure has developed insidiously over months or years may present with many of the clinical features listed in Box 20.7. A consequence of prolonged hypothyroidism is the infiltration of many body tissues by the mucopolysaccharides hyaluronic acid and chondroitin sulphate, resulting in a low-pitched voice, poor hearing, slurred speech due to a large tongue, and compression of the median nerve at the wrist (carpal tunnel syndrome). Infiltration of the dermis gives rise to non-pitting oedema (myxoedema), predominantly in the skin of the hands, feet and eyelids. The resultant periorbital puffiness is often striking and may be combined with facial pallor due to vasoconstriction and anaemia, or a lemon-yellow tint to the skin caused by carotenaemia, along with purplish lips and malar flush. Most cases of hypothyroidism are not clinically obvious and thyroid function testing should be considered in individuals complaining of non-specific symptoms such as tiredness, weight gain, depression or carpal tunnel syndrome.

The key discriminatory features in the history and examination are highlighted in Figure 20.6. Care must be taken to identify patients with transient hypothyroidism, in whom life-long levothyroxine therapy is inappropriate. This may occur during the first 6 months after ^{131}I treatment of Graves disease, in the post-thyrotoxic phase of subacute thyroiditis and in post-partum thyroiditis. In these conditions, levothyroxine treatment is not always necessary, as the patient may be asymptomatic during the short period of thyroid failure.

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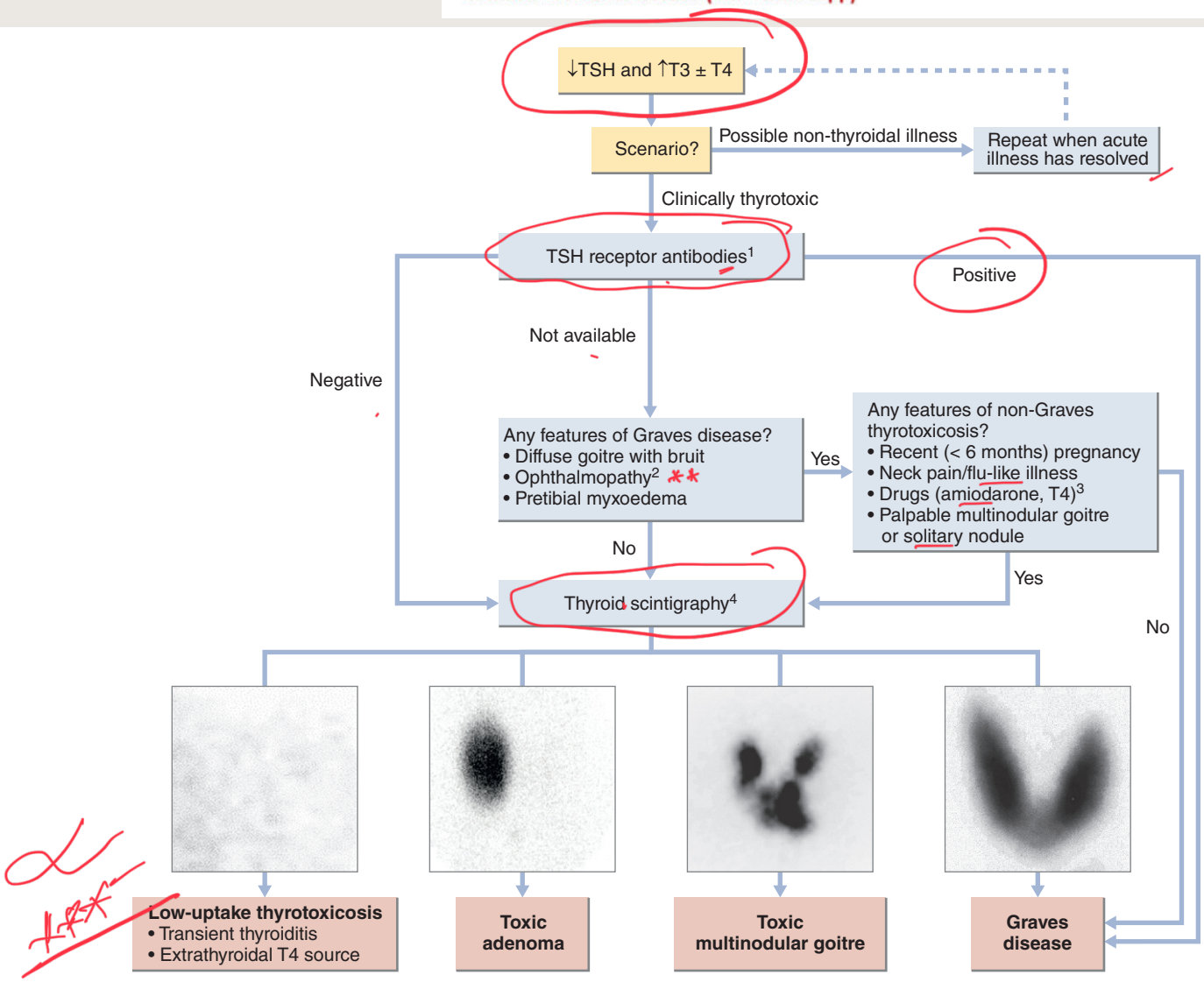

Fig. 20.5 Establishing the differential diagnosis in thyrotoxicosis. [1]Thyroid-stimulating hormone (TSH) receptor antibodies are very rare in patients without autoimmune thyroid disease and occur in ~95% of patients with Graves disease; a positive test is confirmatory, but a negative test does not exclude Graves disease. Other thyroid antibodies (e.g. anti-peroxidase and anti-thyroglobulin antibodies) are unhelpful in the differential diagnosis since they occur frequently in the population and are found with several of the disorders that cause thyrotoxicosis. [2]Graves ophthalmopathy refers to clinical features of exophthalmos and periorbital and conjunctival oedema, not simply the lid lag and lid retraction that can occur in all forms of thyrotoxicosis. [3]Scintigraphy is not necessary in most cases of drug-induced thyrotoxicosis. [4]Technetium-99m (^{99m}Tc) pertechnetate scans of patients with thyrotoxicosis. In low-uptake thyrotoxicosis, most commonly due to a viral, post-partum or iodine-induced thyroiditis, there is negligible isotope detected in the region of the thyroid, although uptake is apparent in nearby salivary glands (not shown here). In a toxic adenoma there is lack of uptake of isotope by the rest of the thyroid gland due to suppression of serum TSH. In multinodular goitre there is relatively low, patchy uptake within the nodules; such an appearance is not always associated with a palpable thyroid. In Graves disease there is diffuse uptake of isotope.

i 20.8 Prevalence of thyroid autoantibodies (%)

	Antibodies to:		
	Thyroid peroxidase[1]	Thyroglobulin	TSH receptor[2]
Normal population	8–27	5–20	<1
Graves disease	50–80	50–70	>95
Autoimmune hypothyroidism	90–100	80–90	10–20
Multinodular goitre	~30–40	~30–40	<1
Transient thyroiditis	~30–40	~30–40	<1

[1]Thyroid peroxidase (TPO) antibodies are the principal component of what was previously measured as thyroid 'microsomal' antibodies.
[2]Thyroid-stimulating hormone receptor antibodies (TRAb) can be agonists (stimulatory, causing Graves thyrotoxicosis) or antagonists ('blocking', causing hypothyroidism).

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Investigations

In the majority of cases, hypothyroidism results from an intrinsic disorder of the thyroid gland (primary hypothyroidism). In this situation, serum T4 is low and TSH is elevated, usually in excess of 20 mIU/L. Measurements of serum T3 are unhelpful since they do not discriminate reliably between euthyroidism and hypothyroidism. Measurement of thyroid peroxidase antibodies is helpful but further investigations are rarely required (see Fig. 20.6). Secondary hypothyroidism (where both TSH and free T4 levels are low) is rare and is caused by failure of TSH secretion in an individual with hypothalamic or anterior pituitary disease. Other non-specific laboratory abnormalities are shown in Box 20.9. In severe, prolonged hypothyroidism, the ECG classically demonstrates sinus bradycardia with low-voltage complexes and may show prolongation of the QRS complex and T-wave flattening or inversion.

i 20.9 Non-specific laboratory abnormalities associated with thyroid dysfunction*

Thyrotoxicosis

- Serum enzymes: raised alanine aminotransferase, γ-glutamyl transferase (GGT), and alkaline phosphatase from liver and bone
- Raised bilirubin
- Mild hypercalcaemia
- Glycosuria: associated diabetes mellitus, 'lag storage' glycosuria

Hypothyroidism

- Serum enzymes: raised creatine kinase, aspartate aminotransferase, lactate dehydrogenase (LDH)
- Hypercholesterolaemia
- Anaemia: normochromic normocytic or macrocytic
- Hyponatraemia

*These abnormalities are not useful in differential diagnosis, so the tests should be avoided and any further investigation undertaken only if abnormalities persist when the patient is euthyroid.

i 20.10 Causes of hypothyroidism

Causes	Anti-TPO antibodies[1]	Goitre[2]
Autoimmune		
Hashimoto thyroiditis	++	±
Spontaneous atrophic hypothyroidism	–	–
Graves disease with TSH receptor-blocking antibodies	+	±
Iatrogenic		
Radioactive iodine ablation	+	±
Thyroidectomy	+	–
Drugs:		
Carbimazole, methimazole, propylthiouracil	+	±
Amiodarone	+	±
Lithium	–	±
Transient thyroiditis		
Subacute (de Quervain) thyroiditis	+	±
Post-partum thyroiditis	+	±
Iodine deficiency		
e.g. In mountainous regions	–	++
Congenital		
Dyshormonogenesis	–	++
Thyroid aplasia	–	–
Infiltrative		
Amyloidosis, Riedel thyroiditis, sarcoidosis etc.	+	++
Secondary hypothyroidism		
TSH deficiency	–	–

[1]As shown in Box 20.8, thyroid autoantibodies are common in the healthy population, so might be present in anyone. ++ high titre; + more likely to be detected than in the healthy population; – not especially likely.
[2]Goitre: – absent; ± may be present; ++ characteristic.
(TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone)

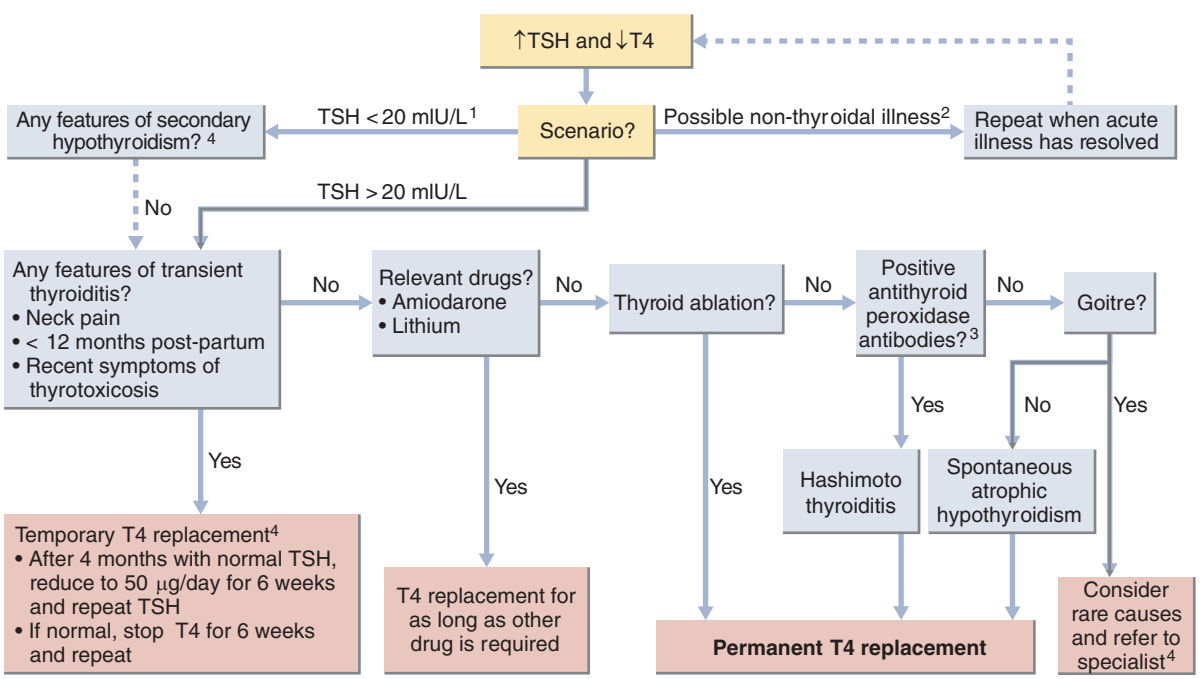

Fig. 20.6 An approach to adults with suspected primary hypothyroidism. This scheme ignores congenital causes of hypothyroidism (see Box 20.10), such as thyroid aplasia and dyshormonogenesis (associated with nerve deafness in Pendred syndrome, p. 709), which are usually diagnosed in childhood. [1]Immunoreactive thyroid-stimulating hormone (TSH) may be detected at normal or even modestly elevated levels in patients with pituitary failure; unless T4 is only marginally low, TSH should be > 20 mIU/L to confirm the diagnosis of primary hypothyroidism. [2]The usual abnormality in 'non-thyroidal illness' is a low TSH but any pattern can occur. [3]Thyroid peroxidase (TPO) antibodies are highly sensitive but not very specific for autoimmune thyroid disease (see Boxes 20.8 and 20.10). [4]Specialist advice is most appropriate where indicated. Secondary hypothyroidism is rare, but is suggested by deficiency of pituitary hormones or by clinical features of pituitary tumour such as headache or visual field defect (p. 734). Rare causes of hypothyroidism with goitre include dyshormonogenesis and infiltration of the thyroid (see Box 20.10).

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Management

Treatment is with levothyroxine replacement. The average replacement dose of levothyroxine is 1.6 µg/kg (100 µg in a 70 kg adult). In healthy younger adults, it is safe to commence an estimated full dose. In older individuals, and those with a history of cardiovascular disease, it is customary to start with a low dose of 25–50 µg per day for 3 weeks before increasing to the estimated full dose. Levothyroxine has a half-life of 7 days and should be taken as a single daily dose. Ten weeks should pass before repeating thyroid function tests and adjusting the dose as TSH takes several weeks to reach a steady state. Symptomatic improvement usually takes 2–3 weeks. Reduction in weight and periorbital puffiness occurs quickly, but the restoration of skin and hair texture and resolution of any effusions may take 3–6 months. As illustrated in Figure 20.6, most patients do not require specialist review but will need life-long levothyroxine therapy.

The dose of levothyroxine should be adjusted to maintain serum TSH within the reference range. To achieve this, serum T4 often needs to be in the upper part of the reference range because the T3 required for receptor activation is derived exclusively from conversion of T4 within the target tissues, without the usual contribution from thyroid secretion. Some physicians advocate combined replacement with T4 (levothyroxine) and T3 (liothyronine) or preparations of animal thyroid extract, but these approaches remain controversial and are not supported by robust evidence. Some patients remain symptomatic despite normalisation of TSH and may wish to take extra levothyroxine, suppressing their TSH. However, a suppressed TSH is a risk factor for osteoporosis and atrial fibrillation (see below; subclinical thyrotoxicosis), so this approach cannot be recommended.

It is important to measure thyroid function every 1–2 years once the dose of levothyroxine is stabilised to assess adherence and allow adjustment for changes in levothyroxine requirements (Box 20.11). Some patients have a persistent elevation of serum TSH despite an ostensibly adequate replacement dose of levothyroxine; most commonly, this is a consequence of suboptimal adherence to therapy. There may be differences in bioavailability between the numerous generic preparations of levothyroxine, and if an individual is experiencing marked changes in serum TSH despite optimal adherence, the prescription of a branded preparation of levothyroxine could be considered. There is some limited evidence that suggests levothyroxine absorption may be better when the drug is taken before bed. In some individuals with variable adherence, levothyroxine is taken diligently or even in excess for a few days prior to a clinic visit, resulting in the seemingly anomalous combination of a high serum T4 and high TSH (see Box 20.5).

20.11 Situations in which an adjustment of the dose of levothyroxine may be necessary

Increased dose required

Pregnancy or oestrogen therapy
- Increases concentration of serum thyroxine-binding globulin

Use of other medication
- Increase T4 clearance: phenobarbital, phenytoin, carbamazepine, rifampicin, sertraline*, chloroquine*
- Interfere with intestinal T4 absorption: colestyramine, sucralfate, aluminum hydroxide, ferrous sulphate, dietary fibre supplements, calcium carbonate

After surgical or ^{131}I ablation of Graves disease
- Reduces thyroidal secretion with time
  Malabsorption

Decreased dose required

Ageing
- Decreases T4 clearance

Graves disease developing in patient with long-standing primary hypothyroidism
- Switch from production of blocking to stimulating TSH receptor antibodies

*Mechanism not fully established.

Levothyroxine replacement in ischaemic heart disease

Hypothyroidism and ischaemic heart disease are common comorbidities. Although angina may remain unchanged in severity or paradoxically disappear with restoration of metabolic rate, exacerbation of myocardial ischaemia, infarction and sudden death are recognised complications of levothyroxine replacement, even using doses as low as 25 µg per day. In patients with known ischaemic heart disease, thyroid hormone replacement should be introduced at low dose and increased very slowly under specialist supervision. Coronary intervention may be required if angina is exacerbated by levothyroxine replacement therapy.

Hypothyroidism in old age

Box 20.12 illustrates some of the diagnostic and management challenges of hypothyroidism in older people.

Hypothyroidism in pregnancy

Women with hypothyroidism usually require an increased dose of levothyroxine in pregnancy; inadequately treated hypothyroidism in pregnancy has been associated with impaired neurodevelopment in the fetus. This is discussed in more detail on page 1308 (see also Box 20.13).

Myxoedema coma

This is a very rare presentation of hypothyroidism in which there is a depressed level of consciousness (not always coma), usually in an older patient who appears myxoedematous. Body temperature may be as low as 25°C, convulsions are not uncommon and cerebrospinal fluid (CSF) pressure and protein content are raised. The mortality rate is 50% and survival depends on early recognition and treatment of hypothyroidism and other factors contributing to the altered consciousness level, such as medication, cardiac failure, infection, hyponatraemia and respiratory failure.

Myxoedema coma is a medical emergency and treatment must begin before biochemical confirmation of the diagnosis. Suspected cases should be treated with 200–400 µg levothyroxine followed by 1.6 µg/kg/day (with the dose reduced by 25% if the IV route is required). Liothyronine 2.5–10 µg every 8 hours may be needed alongside levothyroxine as there may be impaired deiodination in the context of myxoedema. Liothyronine 20 µg every 8 hours could be considered where IV levothyroxine is not available. In survivors, there is a rise in body temperature within 24 hours and, after 48–72 hours, it is usually possible to switch patients to oral levothyroxine in a dose of 1.6 µg/kg daily, with lower doses considered in patients vulnerable to coronary artery disease. Unless it is apparent that the patient has primary hypothyroidism, the thyroid failure should also be assumed to be secondary to hypothalamic or pituitary disease. Empirical treatment with hydrocortisone, pending the results of fT4, TSH and cortisol measurement is recommended (100 mg as intravenous bolus and then 200 mg/day, either as a continuous infusion or in 4 divided doses). Other measures include slow rewarming, cautious use of intravenous

20.12 The thyroid gland in old age

Thyrotoxicosis
- **Causes**: commonly due to multinodular goitre.
- **Clinical features**: apathy, anorexia, proximal myopathy, atrial fibrillation and cardiac failure predominate.
- **Non-thyroidal illness**: thyroid function tests are performed more frequently in older patients but interpretation may be altered by intercurrent illness.

Hypothyroidism
- **Clinical features**: non-specific features, such as physical and mental slowing, are often attributed to increasing age and the diagnosis is delayed.
- **Myxoedema coma**: more likely in older people.
- **Levothyroxine dose**: to avoid exacerbating latent or established heart disease, the starting dose should be 25–50 µg daily. Levothyroxine requirements fall with increasing age and few patients need more than 100 µg daily.
- **Other medication** (see Box 20.10): may interfere with absorption or metabolism of levothyroxine, necessitating an increase in dose.

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20.13 Thyroid disease in pregnancy

Normal pregnancy

- **Trimester-specific reference ranges**: should be used to interpret thyroid function test results in pregnancy.

Iodine deficiency

- **Iodine requirements**: increased in pregnancy. The World Health Organization (WHO) recommends a minimum intake of 250 µg/day.
- **Iodine deficiency**: the major cause of preventable impaired cognitive development in children worldwide.

Hypothyroidism

- **Impaired cognitive development in the offspring**: may be associated with hypothyroidism that is not adequately treated.
- **Levothyroxine replacement therapy dose requirements**: increase by 30%–50% from early in pregnancy. Monitoring to maintain TSH results within the trimester-specific reference range is recommended in early pregnancy and at least once in each trimester.

Thyrotoxicosis

- **Gestational thyrotoxicosis**: associated with multiple pregnancies and hyperemesis gravidarum. Transient and usually does not require antithyroid drug treatment.
- **Graves disease**: the most common cause of sustained thyrotoxicosis in pregnancy.
- **Antithyroid drugs**: propylthiouracil should be used in the first trimester, with carbimazole substituted in the second and third trimesters.

Post-partum thyroiditis

- **Screening**: not recommended for every woman, but thyroid function should be tested 4–6 weeks post partum in those with a personal history of thyroid disease, goitre or other autoimmune disease including type 1 diabetes, in those known to have positive antithyroid peroxidase antibodies, or when there is clinical suspicion of thyroid dysfunction.

fluids, broad-spectrum antibiotics and mechanical ventilation or high-flow oxygen.

Symptoms of hypothyroidism with normal thyroid function tests

The classic symptoms of hypothyroidism are, by their very nature, non-specific (see Box 20.3). There is a wide differential diagnosis for symptoms such as fatigue, weight gain and low mood. As has been noted, outside the context of pituitary and hypothalamic disease, serum TSH is an excellent measure of an individual's thyroid hormone status. However, some individuals believe that they have hypothyroidism despite normal serum TSH concentrations. They require reassurance that their symptoms are being taken seriously and that organic disease has been carefully considered; if their symptoms persist, referral to a team specialising in medically unexplained symptoms should be considered.

Asymptomatic abnormal thyroid function tests

One of the most common problems in medical practice is how to manage patients with abnormal thyroid function tests who have no obvious signs or symptoms of thyroid disease. These can be divided into three categories.

Subclinical thyrotoxicosis

Serum TSH is undetectable and serum T3 and T4 are at the upper end of the reference range. This combination is most often found in older patients with multinodular goitre. These patients are at increased risk of atrial fibrillation and osteoporosis; therapy, either with ^{131}I or low-dose thionamide should be considered. Otherwise, annual review is essential, as the conversion rate to overt thyrotoxicosis is 5% each year.

Subclinical hypothyroidism

Serum TSH is raised and serum T3 and T4 concentrations are at the lower end of the reference range. This may persist for many years, although there is a risk of progression to overt thyroid failure, particularly if antibodies to thyroid peroxidase are present or if the TSH rises above 10 mIU/L. In patients with non-specific symptoms, a trial of levothyroxine therapy may be appropriate. In those with positive autoantibodies or a TSH greater than 10 mIU/L, it is better to treat the thyroid failure early rather than risk loss to follow-up and subsequent presentation with profound hypothyroidism. Levothyroxine should be initiated and titrated as for hypothyroidism.

Non-thyroidal illness ('sick euthyroidism')

This typically presents with a low serum TSH, raised T4 and normal or low T3 in a patient with systemic illness who does not have clinical evidence of thyroid disease. These abnormalities are caused by decreased peripheral conversion of T4 to T3 (with conversion instead to reverse T3), altered levels of binding proteins and their affinity for thyroid hormones, and often reduced secretion of TSH. During convalescence, serum TSH concentrations may increase to levels found in primary hypothyroidism. Treatment is generally not required. As thyroid function tests are difficult to interpret in patients with non-thyroidal illness, it is wise to avoid performing thyroid function tests unless there is clinical evidence of concomitant thyroid disease. If an abnormal result is found, treatment should only be initiated with specialist advice and the diagnosis should be re-evaluated after recovery.

Thyroid lump or swelling

A lump or swelling in the thyroid gland can be a source of considerable anxiety for patients. There are numerous causes but, broadly speaking, a thyroid swelling is either a solitary nodule, a multinodular goitre or a diffuse goitre (Box 20.14; see p. 690).

Nodular thyroid disease is more common in women and occurs in approximately 30% of the adult female population. Most thyroid nodules are impalpable, but may be identified when imaging of the neck is performed for another reason. Palpable thyroid nodules occur in 4%–8% of adult women and 1%–2% of adult men, and classically present when the individual (or their friend or relative) notices a lump in the neck. Multinodular goitre and solitary nodules sometimes present with acute painful enlargement due to haemorrhage into a nodule.

Patients with thyroid nodules often worry that they have cancer, but only 5%–10% of thyroid nodules are malignant. A nodule presenting in childhood or adolescence, particularly if there is a history of head and neck irradiation, or presentation in an older patient should heighten suspicion of a primary thyroid malignancy. The presence of cervical lymphadenopathy also increases the likelihood of malignancy. Rarely, a secondary deposit from a renal, breast or lung carcinoma presents as a painful, rapidly

20.14 Causes of thyroid enlargement

Diffuse goitre

- Simple goitre
- Hashimoto thyroiditis[1]
- Graves disease
- Drugs: iodine, amiodarone, lithium
- Iodine deficiency (endemic goitre)[1]
- Suppurative thyroiditis[2]
- Transient thyroiditis[2]
- Dyshormonogenesis[1]
- Infiltrative: amyloidosis, sarcoidosis etc.
- Riedel thyroiditis[2]

Multinodular goitre

Solitary nodule

- Colloid cyst
- Hyperplastic nodule
- Follicular adenoma
- Papillary carcinoma
- Follicular carcinoma
- Medullary cell carcinoma
- Anaplastic carcinoma
- Lymphoma
- Metastasis

[1]Goitre likely to shrink with levothyroxine therapy.
[2]Usually tender.

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growing, solitary thyroid nodule. Thyroid nodules incidentally identified on FDG PET scanning have an approximately 33% chance of being malignant.

Clinical assessment and investigations

Swellings in the anterior part of the neck most commonly originate in the thyroid and this can be confirmed by demonstrating that the swelling moves on swallowing. There is a broad differential diagnosis of anterior neck swellings, which includes lymphadenopathy, branchial cysts, dermoid cysts and thyroglossal duct cysts (the latter are classically located in the midline and move on protrusion of the tongue).

Free T3, T4 and TSH should be measured in all patients with a goitre or solitary thyroid nodule. The finding of biochemical thyrotoxicosis or hypothyroidism (both of which may be subclinical) should lead to investigations, as already described in Box 20.5 and Figures 20.5 and 20.6.

Thyroid scintigraphy

Thyroid scintigraphy with ^{99m}Tc should be performed in an individual with a low serum TSH and a nodular thyroid to confirm the presence of an autonomously functioning ('hot') nodule (see Fig. 20.5). In such circumstances, further evaluation is not necessary. 'Cold' nodules on scintigraphy have a higher likelihood of malignancy, although the majority are benign.

Thyroid/neck ultrasound

If thyroid function tests are normal, an ultrasound scan will differentiate thyroid lumps from other causes of neck swelling. Ultrasound can establish whether there is generalised or localised swelling of the thyroid. Inflammatory disorders causing a diffuse goitre, such as Graves disease and Hashimoto thyroiditis, demonstrate a diffuse pattern of hypoechogenicity and, in the case of Graves disease, increased thyroid blood flow may be seen on colour-flow Doppler (although ultrasound need not form part of the routine investigation of Graves disease). The presence of thyroid autoantibodies will support the diagnosis of Graves disease or Hashimoto thyroiditis, while their absence in a younger patient with a diffuse goitre and normal thyroid function suggests a diagnosis of 'simple goitre'.

Ultrasound can readily determine the size and number of nodules within the thyroid and can distinguish solid nodules from those with a cystic element. It is used increasingly as the key investigation in defining the risk of malignancy in a nodule and a variety of different grading systems are in use. The size of a nodule is not predictive of malignancy, but hypoechogenicity, intranodular vascularity, the presence of microcalcification and irregular or lobulated margins are associated with increased risk. Purely cystic and 'spongiform'-appearing nodules are highly likely to be benign. Each nodule within a multinodular goitre has the same risk of malignancy as a solitary nodule. Thyroid ultrasonography is a highly specialised investigation and the accurate stratification of risk of malignancy of a thyroid nodule requires skill and expertise.

Fine needle aspiration cytology

Fine needle aspiration cytology is recommended for thyroid nodules that are suspicious for malignancy or are radiologically indeterminate. Fine needle aspiration of a thyroid nodule can be performed in the outpatient clinic, usually under ultrasound guidance. Aspiration may be therapeutic for a cyst, although recurrence on more than one occasion is an indication for surgery or alcohol ablation. Fine needle aspiration cytology cannot differentiate between a follicular adenoma and a follicular carcinoma, and in 10%–20% of cases an inadequate specimen is obtained.

Management

Nodules with a benign appearance on ultrasound may be observed in an ultrasound surveillance programme; when the suspicion of malignancy is very low, the patient may be reassured and discharged. Surgery or radiofrequency ablation may be considered for large, symptomatic nodules. In regions with borderline low iodine intake, there is evidence that levothyroxine therapy, in doses that suppress serum TSH, may reduce the size of some nodules. This should not be routine practice in iodine-sufficient populations.

Nodules that are suspicious for malignancy are treated by surgical excision, by either lobectomy or thyroidectomy. Nodules that are radiologically and/or cytologically indeterminate are more of a management challenge and are often surgically resected. Molecular techniques may, in the future, improve the diagnostic accuracy of thyroid cytology and allow a more conservative strategy for individuals with an indeterminate biopsy. Nodules in which malignancy is confirmed by formal histology are treated as described on page 706.

A diffuse or multinodular goitre may require surgical treatment for cosmetic reasons or if there is compression of local structures (resulting in stridor or dysphagia). ^{131}I therapy can also reduce the size of a multinodular goitre. Levothyroxine therapy may shrink the goitre of Hashimoto disease, particularly if serum TSH is elevated.

Autoimmune thyroid disease

Thyroid diseases are amongst the most prevalent autoimmune diseases and are associated with other organ-specific autoimmune diseases. Autoantibodies may produce inflammation and destruction of thyroid tissue, resulting in hypothyroidism, goitre (in Hashimoto thyroiditis) and sometimes even transient thyrotoxicosis ('Hashitoxicosis'), or they may stimulate the TSH receptor to cause thyrotoxicosis (in Graves disease). There is overlap between these conditions, since some patients have multiple autoantibodies.

Graves disease

Graves disease can occur at any age but is unusual before puberty and most commonly affects women aged 30–50 years. The most common manifestation is thyrotoxicosis with or without a diffuse goitre. The clinical features and differential diagnosis are described on page 694. Graves disease also causes ophthalmopathy and, rarely, pretibial myxoedema (p. 705). These extrathyroidal features usually occur in thyrotoxic patients, but can arise in the absence of thyroid dysfunction.

Graves thyrotoxicosis

Pathophysiology

Thyrotoxicosis results from the production of IgG antibodies directed against the TSH receptors on thyroid follicular cells, which stimulate thyroid hormone production and proliferation of follicular cells, leading to goitre in many patients. These antibodies are termed thyroid-stimulating immunoglobulins (TSI) or TSH receptor antibodies (TRAb) and can be detected in the serum of >95% of patients with Graves disease. The titre of TRAb in the serum is presumed to fluctuate, accounting for the natural history of Graves thyrotoxicosis (Fig. 20.7). Thyroid failure seen in some

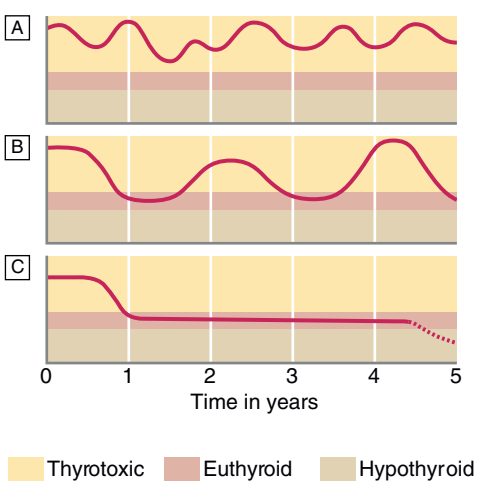

Fig. 20.7 Natural history of the thyrotoxicosis of Graves disease. A and B The majority (60%) of patients have either prolonged periods of thyrotoxicosis of fluctuating severity, or periods of alternating relapse and remission. C It is the minority who experience a single short-lived episode followed by prolonged remission and, in some cases, by the eventual onset of hypothyroidism.

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patients may result from the presence of blocking antibodies against the TSH receptor and from tissue destruction by cell-mediated immunity.

Graves disease has a strong genetic component. There is 20%–40% concordance for thyrotoxicosis between monozygotic twins, but only 5% concordance between dizygotic twins. Genome-wide association studies have identified several genes associated with susceptibility. These include *HLA-DRβ-Arg74*, *CTLA4*, *PTPN22*, *TSHR*, *CD25* and *CD40*. Many of these loci have been implicated in the pathogenesis of other autoimmune diseases.

In most cases the environmental trigger for Graves disease is not apparent. In regions of iodine deficiency, iodine supplementation can precipitate thyrotoxicosis in those with pre-existing subclinical Graves disease. Smoking is associated with an approximately twofold risk of Graves thyrotoxicosis and approximately sevenfold risk of the development of ophthalmopathy.

Management

Symptoms of thyrotoxicosis respond to β-blockade but definitive treatment requires control of thyroid hormone secretion. The different options are compared in Box 20.15. Some clinicians adopt an empirical approach of prescribing a course of antithyroid drug therapy and then recommending ^{131}I or surgery if relapse occurs. However, ^{131}I is also used extensively as a first-line therapy, given the high risk of relapse following a course of antithyroid drugs (>60%). Observational studies have linked therapeutic ^{131}I with increased incidence of some malignancies, particularly of the thyroid and gastrointestinal tract, but results are inconsistent; the association may be with Graves disease rather than its therapy, and the magnitude of the effect, if any, is small. Experience from the disaster at the Chernobyl nuclear power plant in 1986 suggests that younger people are more sensitive to radiation-induced thyroid cancer.

Antithyroid drugs The most commonly used are carbimazole and its active metabolite, methimazole (not available in the UK). Propylthiouracil is equally effective. These drugs reduce the synthesis of new thyroid hormones by inhibiting the iodination of tyrosine (see Fig. 20.3). Carbimazole may also have an immunosuppressive action, leading to a reduction in serum TRAb concentrations, but this does not significantly influence the natural history of the thyrotoxicosis.

Antithyroid drugs are typically introduced at high doses (carbimazole 20–40 mg daily or propylthiouracil 200–400 mg daily), although lower doses are reasonable in individuals with only modest elevation of T4 and T3. Usually, this results in subjective improvement within 10–14 days and renders the patient clinically and biochemically euthyroid at 6–8 weeks. At this point, the dose can be down-titrated to maintain T4 and TSH within their reference range. In most patients, carbimazole is continued at 5–20 mg per day for 12–18 months in the hope that remission will occur. 50%–80% of patients with Graves disease will subsequently relapse, usually within 2 years of stopping treatment. Risk factors for relapse include younger age, male sex, presence of a goitre and higher TRAb titres at both diagnosis and cessation of antithyroid therapy. Rarely, T4 and TSH levels fluctuate between those of thyrotoxicosis and hypothyroidism at successive review appointments, despite good drug adherence, presumably due to rapidly changing concentrations of TRAb. In these patients, satisfactory control can be achieved by blocking thyroid hormone synthesis with carbimazole 20–40 mg daily and adding levothyroxine 1.6 μg/kg daily as replacement therapy (a 'block and replace' regimen).

Antithyroid drugs can have adverse effects. The most common is a rash. Agranulocytosis is a rare but potentially serious complication (1–2 per 1000) that cannot be predicted by routine measurement of white blood cell count, but which is generally reversible on stopping treatment. Patients should be warned to stop the drug and seek medical advice immediately should a severe sore throat, mouth ulcers or fever develop while on treatment. Carbimazole crosses the placenta and has a small risk of inducing congenital malformations including aplasia cutis, a localised defect in skin development (it should be avoided during the first trimester of pregnancy). Propylthiouracil is associated with a small risk of hepatotoxicity, which, in some instances, has resulted in liver failure requiring liver transplantation, and even in death. It should therefore be considered second-line therapy to carbimazole, used only during pregnancy or if an adverse reaction to carbimazole has occurred, and patients should be monitored for hepatotoxicity.

Thyroid surgery Patients should be rendered euthyroid with antithyroid drugs before surgery. Oral potassium iodide, ~50–100 mg (e.g. 1–2 drops [0.05–0.1 mL] saturated solution of potassium iodide) 3 times daily, is often added for 10 days before surgery to limit perioperative thyroid hormone release and reduce the size and vascularity of the gland, making surgery technically easier. The optimal surgical approach is a 'near-total' thyroidectomy, leaving behind only a small portion of gland adjacent to the recurrent laryngeal nerves. This strategy results in permanent hypothyroidism and is probably associated with a higher risk of hypoparathyroidism, compared to 'subtotal' thyroidectomy, but maximises the potential for cure of thyrotoxicosis.

Radioactive iodine ^{131}I is administered orally as a single dose and is trapped and organified in the thyroid (see Fig. 20.3). ^{131}I emits both β and γ radiation and, although it decays within a few weeks, it has long-lasting

i 20.15 Comparison of treatments for the thyrotoxicosis of Graves disease

Management	Common indications	Contraindications	Disadvantages/complications
Antithyroid drugs (carbimazole, propylthiouracil)	First episode in patients < 40 years	Breastfeeding[1]	Hypersensitivity rash 2% Agranulocytosis 0.2% Hepatotoxicity (with propylthiouracil) – very rare but potentially fatal >50% relapse rate usually within 2 years of stopping drug
Thyroidectomy	Large goitre Poor drug adherence, especially in young patients Recurrent thyrotoxicosis after course of antithyroid drugs in young patients	Previous thyroid surgery Dependence on voice, e.g. singer, lecturer[2]	Hypothyroidism (~25%) Transient hypocalcaemia (10%) Permanent hypoparathyroidism (1%) Recurrent laryngeal nerve palsy[2] (1%)
Radio-iodine	Patients > 40 years[3] Recurrence following surgery irrespective of age Other serious comorbidity	Pregnancy or planned pregnancy within 6 months of treatment Active Graves ophthalmopathy[4]	Hypothyroidism: ~40% in first year, 80% after 15 years Most likely treatment to result in exacerbation of ophthalmopathy[4]

[1] Antithyroid drugs, particularly carbimazole, pass into breast milk. Risks/benefits should be considered with a specialist and as low a dose as possible chosen if necessary.
[2] It is not only vocal cord palsy due to recurrent laryngeal nerve damage that alters the voice following thyroid surgery; the superior laryngeal nerves are frequently transected and this results in minor changes in voice quality.
[3] In many institutions, ^{131}I is used more liberally and is prescribed for much younger patients.
[4] The extent to which radio-iodine exacerbates ophthalmopathy is controversial and practice varies; some use prednisolone to reduce this risk.

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inhibitory effects on survival and replication of follicular cells. In most centres, approximately 400–600 MBq (approximately 10–15 mCi) is administered. This regimen is effective in 75% of patients within 4–12 weeks. Following treatment, symptoms can be controlled by β-blockade or, in more severe cases, by carbimazole. Carbimazole reduces the efficacy of ^{131}I therapy because it prevents organification of ^{131}I in the gland, and so should be avoided until 48 hours after ^{131}I administration. If thyrotoxicosis persists after 6 months, a further dose of ^{131}I can be given. If successful, in the context of Graves disease, ^{131}I treatment will likely render the patient hypothyroid. Due to the difficulty predicting thyroid dysfunction following ^{131}I therapy, and the risk of delay diagnosing hypothyroidism, some physicians advocate initiation of 'block and replace' treatment for 6 months following ^{131}I, with subsequent withdrawal of thionamide. ^{131}I is usually avoided in patients with Graves ophthalmopathy and evidence of significant active orbital inflammation. It can be administered with caution in those with mild or 'burnt-out' eye disease, when it is customary to cover the treatment with a 6-week tapering course of oral prednisolone. In women of reproductive age, pregnancy must be excluded before administration of ^{131}I and avoided for at least 6 months thereafter. Men are also advised to use strict contraceptive measures for at least 4 months after receiving ^{131}I, to avoid the possibility of conceiving with sperm that have been exposed to radiation.

Thyrotoxicosis in pregnancy Thyrotoxicosis in pregnancy may be associated with significant maternal and fetal morbidity. Management is specialised and is discussed on page 1308 (see also Box 20.13).

Thyrotoxicosis in adolescence Thyrotoxicosis can occasionally occur in adolescence and is almost always due to Graves disease. The presentation may be atypical and management challenging, as summarised in Box 20.16.

Graves ophthalmopathy

This condition is immunologically mediated, with the TSH receptor identified as the main autoantigen. Cytokine-mediated proliferation of fibroblasts that secrete hydrophilic glycosaminoglycans occurs in the orbit and dermis. The resulting increase in interstitial fluid content, combined with a chronic inflammatory cell infiltrate, causes marked swelling and ultimately fibrosis of the extraocular muscles (Fig. 20.8) and a rise in retrobulbar pressure. The eye is displaced forwards (proptosis, exophthalmos) and in severe cases there is optic nerve compression.

Ophthalmopathy, like thyrotoxicosis (see Fig. 20.7), typically follows an episodic course and it is helpful to distinguish patients with active inflammation (periorbital oedema and conjunctival inflammation with changing orbital signs) from those in whom the inflammation has 'burnt out'. Eye disease is detectable in up to 50% of thyrotoxic patients at presentation (although moderate to severe in only 5%), but active ocular inflammation may occur before or after thyrotoxic episodes (exophthalmic Graves disease). Ophthalmopathy is more common in men and cigarette smokers. It may be exacerbated by ^{131}I and poor control of thyroid function, especially hypothyroidism. The most frequent presenting symptoms are related to increased exposure of the cornea, resulting from proptosis and lid retraction. There may be excessive lacrimation made worse by wind and bright light, a 'gritty' sensation in the eye and pain due to conjunctivitis or corneal ulceration. In addition, there may be reduction of visual acuity and/or visual fields because of corneal oedema or optic nerve compression. Other signs of optic nerve compression include reduced colour vision and a relative afferent pupillary defect (see p. 691). If the extraocular muscles are involved and do not act in concert, diplopia results.

Most patients require no treatment other than reassurance. Smoking cessation should be strongly encouraged. Methylcellulose eye drops and gel counter the gritty discomfort of dry eyes, and tinted glasses or side shields reduce the excessive lacrimation triggered by sun or wind. In patients with mild Graves ophthalmopathy, oral selenium (100 μg twice daily for 6 months) improves quality of life, reduces ocular involvement and slows progression of disease. Moderate to severe ophthalmopathy is optimally managed by an expert multidisciplinary service. More severe inflammatory episodes are treated with glucocorticoids (e.g. pulsed intravenous methylprednisolone) and immunosuppressive therapies (e.g. rituximab and tocilizumab); the insulin-like growth factor-1 (IGF-1) receptor inhibitor teprotumumab may be required in moderate to severe ophthalmopathy. Orbital radiotherapy may also be considered. Loss of visual acuity is an indication for urgent surgical decompression of the orbit. In 'burnt-out' disease, surgery to the extraocular muscles, and later the eyelids, may improve diplopia, conjunctival exposure and cosmetic appearance.

Pretibial myxoedema

This infiltrative dermopathy occurs in fewer than 5% of patients with Graves disease and has similar pathological features as occur in the orbit. It takes the form of raised pink-coloured or purplish plaques on the anterior aspect of the leg, extending on to the dorsum of the foot; less commonly, the face and arms are affected (see p. 690). The lesions may be itchy and the skin may have a 'peau d'orange' appearance with growth of coarse hair. Treatment is rarely required but in severe cases topical glucocorticoids may be helpful.

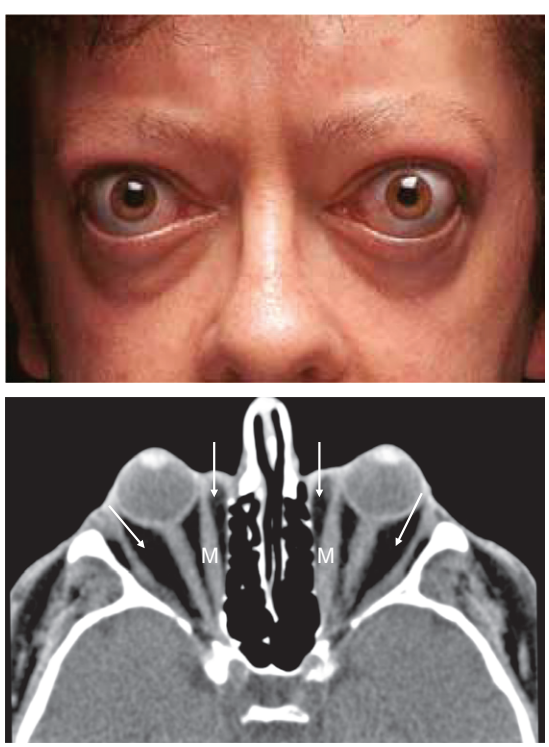

Fig. 20.8 Graves disease. A Bilateral ophthalmopathy in a 42-year-old man. The main symptoms were diplopia in all directions of gaze and reduced visual acuity in the left eye. The periorbital swelling is due to retrobulbar fat prolapsing into the eyelids, and increased interstitial fluid as a result of raised intraorbital pressure. B Axial CT of the orbits, showing bilateral increased intraorbital fat (arrows), proptosis and bilateral enlarged medial recti muscles (M).

20.16 Thyrotoxicosis in adolescence

- **Presentation**: may present with a deterioration in school performance or symptoms suggestive of attention deficit hyperactivity disorder.
- **Antithyroid drug therapy**: prolonged courses may be required because remission rates following an 18-month course of therapy are much lower than in adults.
- **Adherence**: adherence to antithyroid drug therapy is often suboptimal, resulting in poor disease control that may adversely affect performance at school.
- **Radio-iodine therapy**: usually avoided in adolescents because of concerns about risk of future malignancy.

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Hashimoto thyroiditis

Hashimoto thyroiditis (or 'chronic autoimmune thyroiditis') is characterised by destructive lymphocytic infiltration of the thyroid, ultimately leading to a varying degree of fibrosis and thyroid enlargement. It has atrophic and goitrous variants.

Hashimoto thyroiditis increases in incidence with age and affects approximately 3.5 per 1000 women and 0.8 per 1000 men each year. Many present with a small or moderately sized diffuse goitre, which is characteristically firm or rubbery in consistency. Around 25% of patients are hypothyroid at presentation. In the remainder, serum T4 is normal and TSH normal or raised, but these patients are at risk of developing overt hypothyroidism in future years. Antibodies against thyroid peroxidase (TPO) are present in the serum in more than 90% of patients with Hashimoto thyroiditis. Thyroid lymphoma is more common in patients with Hashimoto thyroiditis, although is exceedingly rare with an incidence of 2 cases per million per year.

Levothyroxine therapy is indicated as treatment for hypothyroidism and to shrink an associated goitre. In this context, the dose of levothyroxine should be sufficient to suppress serum TSH to low but detectable levels.

Transient thyroiditis

Subacute (de Quervain) thyroiditis

In its classical painful form, subacute thyroiditis is a transient inflammation of the thyroid gland occurring after viral infection. There is pain in the region of the thyroid that may radiate to the angle of the jaw and the ears, and is made worse by swallowing, coughing and movement of the neck. The thyroid is usually palpably enlarged and tender. Systemic upset is common. Affected patients are usually females aged 20–40 years. Painless transient thyroiditis can also occur after viral infection and in patients with underlying autoimmune disease. The condition can also be precipitated by drugs, including interferon-α and lithium.

Irrespective of the clinical presentation, inflammation in the thyroid gland is associated with release of colloid and stored thyroid hormones, damage to follicular cells and impaired synthesis of new thyroid hormones. As a result, T4 and T3 levels are raised for 4–6 weeks whilst the pre-formed colloid is depleted. Thereafter, there is usually a period of hypothyroidism of variable severity before the follicular cells recover and normal thyroid function is restored within 4–6 months (Fig. 20.9). In the thyrotoxic phase, the iodine uptake is low because the damaged follicular cells are unable to trap iodine and because TSH secretion is suppressed. Low-titre thyroid autoantibodies appear transiently in the serum, and the erythrocyte sedimentation rate (ESR) is usually raised. High-titre autoantibodies suggest an underlying autoimmune pathology and greater risk of recurrence and ultimate progression to hypothyroidism.

Pain and systemic symptoms usually respond to simple measures such as non-steroidal anti-inflammatory drugs (NSAIDs). Occasionally, however, it may be necessary to prescribe prednisolone 40 mg daily for 2–4 weeks (a lower dose of 15 mg may also be effective). The thyrotoxicosis is mild and treatment with a β-blocker is usually adequate. Antithyroid drugs are of no benefit because thyroid hormone synthesis is impaired rather than enhanced. Careful monitoring of thyroid function and symptoms is required so that levothyroxine can be prescribed temporarily if needed during the hypothyroid phase. Care must be taken to identify patients presenting with hypothyroidism who are in this late stage of transient thyroiditis, since they are unlikely to require life-long levothyroxine therapy (see Fig. 20.6). In this context a normal TSH 6 weeks following reduction of the dose of levothyroxine to 50 μg/day indicates it should be possible to withdraw treatment.

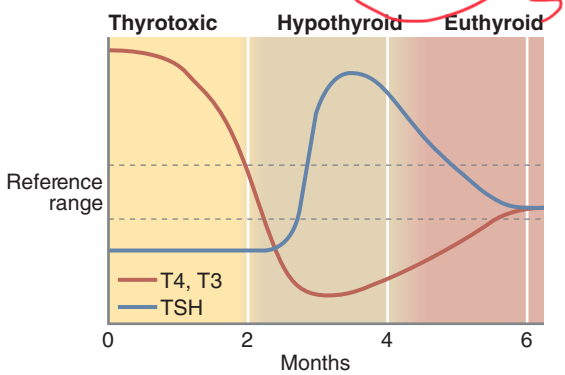

Fig. 20.9 Thyroid function tests in an episode of transient thyroiditis. This pattern might be observed in classical subacute (de Quervain) thyroiditis, painless thyroiditis or post-partum thyroiditis. The duration of each phase varies between patients. (T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone)

Post-partum thyroiditis

The maternal immune response, which is attenuated during pregnancy to allow survival of the fetus, is enhanced after delivery, and may unmask previously unrecognised subclinical autoimmune thyroid disease. Surveys have shown that transient biochemical disturbances of thyroid function occur in 5%–10% of women within 6 months of delivery (see Box 20.13). Those affected are likely to have antithyroid peroxidase antibodies in the serum in early pregnancy. Symptoms of thyroid dysfunction are rare and there is no association between postnatal depression and abnormal thyroid function tests. However, symptomatic thyrotoxicosis presenting for the first time within 12 months of childbirth is likely to be due to post-partum thyroiditis and the diagnosis is confirmed by negligible ^{99m}Tc uptake (breast milk should be discarded temporarily following the scan). The clinical course and treatment are similar to those of painless subacute thyroiditis (see above). Post-partum thyroiditis tends to recur after subsequent pregnancies (see also Box 20.13).

Iodine-associated thyroid disease

Iodine deficiency

Iodine is an essential micronutrient and is a key component of thyroid hormones. The World Health Organization (WHO) recommends a daily intake of iodine of 150 μg/day for adult men and women; higher levels are recommended for pregnant women (see p. 1308) as iodine deficiency is associated with impaired fetal brain development, and severe deficiency can cause cretinism. Dietary sources of iodine include seafood, dairy products, eggs and grains. Dietary iodine deficiency is a global public health issue, with an estimated one-third of the world population living in areas of iodine insufficiency. Iodine deficiency is particularly common in Central Africa, South-east Asia and the Western Pacific. It is associated with the development of thyroid nodules and goitre (endemic goitre): the reduced substrate available for thyroid hormone production increases thyroid gland activity to maximise iodine uptake and recycling, and this acts as a potent stimulus for enlargement of the thyroid and nodule formation. Most affected patients are euthyroid with normal or raised TSH levels, although hypothyroidism can occur with severe iodine deficiency. Suspected iodine deficiency can be assessed by measuring iodine in urine (either a 24-hour collection or a spot sample). Endemic goitre can be treated by iodine supplementation, and a reduction in nodule and goitre size can be seen, particularly if it is commenced in childhood. Iodine deficiency is not associated with an increased risk of Graves disease or thyroid cancer, but the high prevalence of nodular autonomy does result in an increased risk of thyrotoxicosis and this risk may be further increased by iodine supplementation. Conversely, iodine supplementation may also increase the prevalence of subclinical hypothyroidism and autoimmune hypothyroidism. These complex effects of iodine supplementation are further discussed below.

Iodine-induced thyroid dysfunction

Iodine has complex effects on thyroid function. Very high concentrations of iodine inhibit thyroid hormone synthesis and release (known as the Wolff–Chaikoff effect) and this forms the rationale for iodine treatment in thyroid

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crisis and prior to thyroid surgery for thyrotoxicosis. This is an autoregulatory response thought to protect the body from the sudden release of large amounts of thyroid hormone in response to the ingestion of a substantial load of iodine. This effect only lasts for about 10 days, after which it is followed by an 'escape phenomenon': essentially, the return to normal organification of iodine and thyroid peroxidase action (see Fig. 20.3). Therefore, if iodine is given to prepare an individual with Graves disease for surgery, the operation must happen within 10–14 days; otherwise, a significant relapse of the thyrotoxicosis could occur.

Both iodine deficiency and underlying thyroid disease moderate the effects of iodine on thyroid function. In iodine-deficient parts of the world, transient thyrotoxicosis may be precipitated by prophylactic iodinisation programmes. In iodine-sufficient areas, thyrotoxicosis can be precipitated by iodine-containing radiographic contrast medium or expectorants in individuals who have underlying multinodular goitre or Graves disease in remission. Induction of thyrotoxicosis by iodine is called the Jod–Basedow effect. Chronic excess iodine administration can also result in hypothyroidism; this is, in effect, a failure to escape from the Wolff–Chaikoff effect and usually occurs in the context of prior insult to the thyroid by autoimmune disease, thyroiditis, exposure to lithium or antithyroid drugs, or surgery.

Amiodarone

The anti-arrhythmic agent amiodarone has a structure that is analogous to that of T4 (Fig. 20.10) and contains copious iodine; a 200 mg dose contains 75 mg iodine. Amiodarone has a cytotoxic effect on thyroid follicular cells and inhibits the conversion of T4 to T3 (increasing the ratio of T4:T3). Most patients receiving amiodarone have normal thyroid function, but up to 20% develop hypothyroidism or thyrotoxicosis and so thyroid function should be monitored regularly. TSH provides the best indicator of thyroid function.

The thyrotoxicosis can be classified as either:

- *type I*: iodine-induced excess thyroid hormone synthesis in patients with an underlying thyroid disorder, such as nodular goitre or latent Graves disease (an example of the Jod–Basedow effect), or
- *type II*: thyroiditis due to a direct cytotoxic effect of amiodarone administration.

These patterns can overlap and may be difficult to distinguish clinically. There is no widely accepted management algorithm, although the iodine excess renders the gland resistant to ^{131}I. Antithyroid drugs may be effective in patients with the type I form but are ineffective in type II thyrotoxicosis. Prednisolone is beneficial in the type II form. A pragmatic approach is to commence combination therapy with carbimazole and prednisolone in patients with significant thyrotoxicosis. A rapid response (within 1–2 weeks) usually indicates a type II picture and permits withdrawal of carbimazole; a slower response suggests a type I picture, in which case carbimazole may be continued and prednisolone withdrawn. If the cardiac state allows, amiodarone should be discontinued, but it has a long half-life (50–60 days) and so its effects are long-lasting. To minimise the risk of type I thyrotoxicosis, thyroid function should be measured in all patients prior to commencement of amiodarone therapy and amiodarone should be avoided if TSH is suppressed.

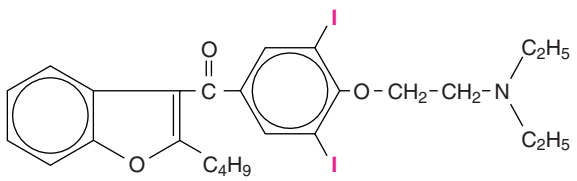


Fig. 20.10 The structure of amiodarone. Note the similarities to thyroxine (T4) (see Fig. 20.3).

Hypothyroidism should be treated with levothyroxine, which can be given with amiodarone and may need to be continued in the long term.

Simple and multinodular goitre

These terms describe diffuse or multinodular enlargement of the thyroid, which occurs sporadically and is of unknown aetiology.

Simple diffuse goitre

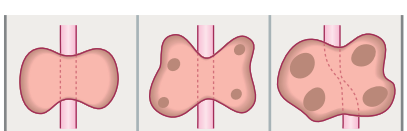
This form of goitre usually presents between the ages of 15 and 25 years, often during pregnancy, and tends to be noticed by friends and relatives rather than the patient. Occasionally, there is a tight sensation in the neck, particularly when swallowing. The goitre is soft and symmetrical, and the thyroid enlarged to two or three times normal. There is no tenderness, lymphadenopathy or overlying bruit. Concentrations of free T3, free T4 and TSH are normal and no thyroid autoantibodies are detected in the serum. No treatment is necessary and the goitre usually regresses. In some, however, the unknown stimulus to thyroid enlargement persists and, because of recurrent episodes of hyperplasia and involution during the following 10–20 years, the gland becomes multinodular with areas of autonomous function.

Multinodular goitre

The natural history is shown in Figure 20.11. Patients with thyroid enlargement in the absence of thyroid dysfunction or positive autoantibodies (i.e. with 'simple goitre'; see above) as young adults may progress to develop nodules. These nodules grow at varying rates and secrete thyroid hormone 'autonomously', thereby suppressing TSH-dependent growth and function in the rest of the gland. Ultimately, complete suppression of TSH occurs in about 25% of cases, with T4 and T3 levels often within the reference range (subclinical thyrotoxicosis), but sometimes elevated (toxic multinodular goitre; see Fig. 20.5).

Clinical features and investigations

Multinodular goitre is usually diagnosed in patients presenting with a large goitre with or without tracheal compression, a sudden painful swelling caused by haemorrhage into a nodule or cyst or with thyrotoxicosis. The goitre is nodular or lobulated on palpation and may extend retrosternally; however, not all multinodular goitres are easily palpable. Very large goitres can cause mediastinal compression with stridor (Fig. 20.12), dysphagia and obstruction of the superior vena cava. Hoarseness due to recurrent laryngeal nerve palsy can occur but is far more suggestive of thyroid carcinoma.



Age (in years)	15–25	26–55	> 55
Goitre	Diffuse	Nodular	Nodular
Tracheal compression/ deviation	No	Minimal	Yes
T3, T4	Normal	Normal	Raised
TSH	Normal	Normal or undetectable	Undetectable

Fig. 20.11 Natural history of simple goitre. (T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone)

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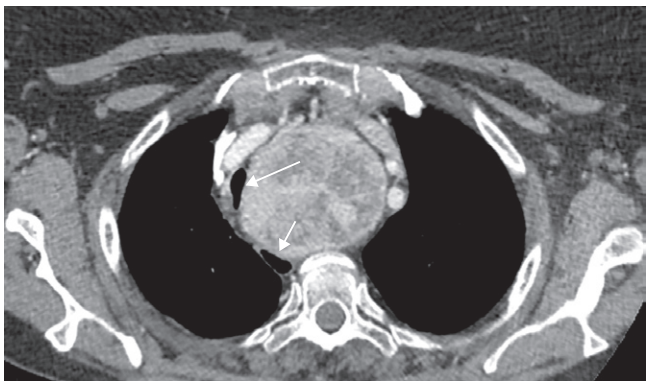

Fig. 20.12 Retrosternal goitre. CT showing retrosternal goitre compressing and displacing the trachea (long arrow) to the right with significant luminal narrowing resulting in breathlessness and stridor. The oesophagus (short arrow) is also displaced to the right.

The diagnosis can be confirmed by ultrasonography and/or thyroid scintigraphy (see Fig. 20.5). In symptomatic patients with large goitres, a flow-volume loop and barium swallow can identify significant tracheal or oesophageal compression, respectively (see Fig. 17.7). If intervention is contemplated, computed tomography (CT) or magnetic resonance imaging (MRI) of the thoracic inlet should be performed to quantify the degree of tracheal displacement or compression and the extent of retrosternal extension. Nodules should be evaluated for the possibility of thyroid neoplasia.

Management

If the goitre is small, no treatment is necessary but annual thyroid function testing should be arranged, as the natural history is progression to a toxic multinodular goitre. Thyroid surgery is indicated for large goitres that cause mediastinal compression or that are cosmetically unattractive. ^{131}I can result in some reduction in thyroid size and may be of value in older patients. Levothyroxine therapy is of no benefit in shrinking multinodular goitres in iodine-sufficient countries and may simply aggravate any associated thyrotoxicosis.

In toxic multinodular goitre, treatment is usually with ^{131}I. The iodine uptake is lower than in Graves disease, so a higher dose may be administered (up to 800 Mbq (approximately 20 mCi)); resultant hypothyroidism is less common. In thyrotoxic patients with a large goitre, thyroid surgery may be indicated. Long-term treatment with antithyroid drugs is not usually employed, as relapse is invariable after drug withdrawal; drug therapy is normally reserved for frail older patients in whom surgery or ^{131}I is not an appropriate option.

Asymptomatic patients with subclinical thyrotoxicosis may be offered ^{131}I or surgery on the grounds that a suppressed TSH is a risk factor for atrial fibrillation and, particularly in post-menopausal women, osteoporosis.

Thyroid neoplasia

Patients with thyroid neoplasms usually present with a solitary nodule. Most are benign and a few of these, called 'toxic adenomas', secrete excess thyroid hormones. Primary thyroid malignancy is rare, accounting for less than 1% of all carcinomas, and has a global age standardised incidence of 10.1 per 100,000 women and 3.1 per 100,000 men per year. As shown in Box 20.17, it can be classified according to the cell type of origin. With the exception of medullary carcinoma, thyroid cancer is more common in females. Thyroid neoplasms often have identifiable somatic mutations in genes such as *BRAF* (papillary, anaplastic), *TERT* (follicular), *RAS* (follicular), *RET* (papillary and medullary), *p53* (anaplastic). Identification of molecular abnormalities may aid in diagnosis and prognostication, and may identify targets for therapy in advanced disease.

i 20.17 Malignant thyroid tumours

Type of tumour	Frequency (%)	Age at presentation (years)	5-year survival (%)
Follicular cells			
Differentiated carcinoma:			
Papillary	75–85	20–40	>99
Follicular	10–20	40–60	98
Anaplastic	<5	>60	10
Parafollicular C cells			
Medullary carcinoma	5–8	>40*	93
Lymphocytes			
Lymphoma	<5	>60	71

*Patients with medullary carcinoma as part of multiple endocrine neoplasia (MEN) types 2a and 2b (p. 742) may present in childhood.

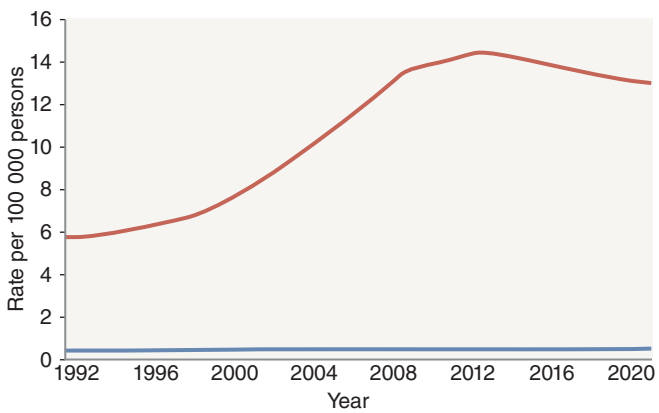

Fig. 20.13 Incidence and death rates of thyroid cancer in the USA. Although the incidence (red line) has increased from 1990 because of higher rates of discovery due to the use of more imaging, the overall death rate (blue line) remains very low with an overall 5-year survival of >98%. *From National Cancer Institute: https://seer.cancer.gov/statfacts/html/thyro.html.*

Toxic adenoma

A solitary toxic nodule is the cause of less than 5% of all cases of thyrotoxicosis. The nodule is a follicular adenoma, which autonomously secretes excess thyroid hormones and inhibits endogenous TSH secretion, with subsequent atrophy of the rest of the thyroid gland. The adenoma is usually greater than 3 cm in diameter.

Most patients are female and over 40 years of age. Although many nodules are palpable, the diagnosis can be made with certainty only by thyroid scintigraphy (see Fig. 20.5). The thyrotoxicosis is usually mild and in almost 50% of patients the plasma T3 alone is elevated (T3 thyrotoxicosis). ^{131}I (400–800 MBq (10–20 mCi)) is highly effective and is an ideal treatment since the atrophic cells surrounding the nodule do not take up iodine and so receive little or no radiation. For this reason, permanent hypothyroidism is unusual. Hemithyroidectomy is an alternative management option.

Differentiated carcinoma

The incidence of thyroid carcinoma has increased significantly since the early 1990s, although this has not been paralleled by any significant increase in thyroid carcinoma deaths over the same period (Fig. 20.13). Increasing incidence of thyroid carcinoma is, at least in part, explained by an increased rate of incidental detection, because of greater use of neck imaging.

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Papillary carcinoma

This is the most common of the malignant thyroid tumours and accounts for 90% of radiation-induced thyroid cancer. It may be multifocal and spread is initially to regional lymph nodes. Some patients present with cervical lymphadenopathy and no apparent thyroid enlargement; in such instances, the primary lesion may be less than 10 mm in diameter.

Follicular carcinoma

This is usually a single encapsulated lesion. Spread to cervical lymph nodes is rare. Metastases are blood-borne and are most often found in bone, lungs and brain.

Management

The management of thyroid cancers should be individualised and planned in multidisciplinary team meetings that may include thyroid surgeons, endocrinologists, oncologists, pathologists, radiologists and nurse specialists. Large tumours, those with adverse histological features and/or tumours with metastatic disease at presentation are usually managed by total thyroidectomy (either as a single operation or a lobectomy followed by completion thyroidectomy) followed by a large dose of ^{131}I (1100 or 3700 MBq (approximately 30 or 100 mCi)) to ablate any remaining normal or malignant thyroid tissue. Depending on risk of recurrence, levothyroxine doses sufficient to suppress TSH may be required. Smaller tumours with no adverse histological features may require only thyroid lobectomy.

Follow-up involves measurement of serum thyroglobulin, which should be undetectable in patients whose normal thyroid has been ablated by ^{131}I and who are taking a suppressive dose of levothyroxine. Thyroglobulin antibodies may interfere with the assay and, depending on the method employed, may falsely increase or decrease the result. Detectable thyroglobulin, in the absence of assay interference, is suggestive of tumour recurrence or metastasis, particularly if the thyroglobulin titre is rising across serial measurements. Locally recurrent or metastatic disease may be identified by ultrasound, CT, MRI and/or whole-body scanning with ^{131}I, and may be treated with further surgery and/or ^{131}I therapy. ^{131}I treatment in thyroid cancer and isotope scanning both require serum TSH concentrations to be elevated (> 20 mIU/L). This may be achieved by administering intramuscular recombinant human TSH or by levothyroxine withdrawal for 3–4 weeks, inducing symptomatic hypothyroidism. The former approach is more acceptable to patients, but it is more expensive. Those with locally advanced or metastatic papillary and follicular carcinoma that is refractive to ^{131}I may be considered for therapy with sorafenib, lenvatinib or vandetanib. These drugs are multi-targeted tyrosine kinase inhibitors and have been shown in trials to prolong progression-free survival by between 5 and 14 months. They have multiple toxicities, however, including poor appetite, weight loss, fatigue, diarrhoea, mucositis, rashes, hypertension and blood dyscrasias. The potential benefits of therapy should therefore be weighed carefully against side-effects that could significantly impair quality of life. Selpercatinib, a RET inhibitor, may also be used in advanced disease where a *RET* mutation has been identified on molecular analysis.

Prognosis

Most patients with papillary and follicular thyroid cancer are cured with appropriate treatment. Adverse prognostic factors include older age at presentation, the presence of distant metastases, male sex and certain histological subtypes. ^{131}I therapy can be effective in treating those with distant metastases, particularly small-volume disease in the lungs, and prolonged survival is quite common.

Anaplastic carcinoma and lymphoma

These two conditions are difficult to distinguish clinically but are cytologically and histologically distinct. Patients are usually over 60 years of age and present with rapid thyroid enlargement over 2–3 months. The goitre is hard and there may be stridor due to tracheal compression and hoarseness due to recurrent laryngeal nerve palsy. For many patients there is no effective treatment for anaplastic carcinoma, although surgery and radiotherapy may be considered in some circumstances. In older patients, median survival is only 7 months. There are reports of survival benefit using dabrafenib (a BRAF inhibitor) and trametinib (a kinase inhibitor) in tumours where a *BRAF* mutation has been identified.

The prognosis for lymphoma, which may arise from pre-existing Hashimoto thyroiditis, is better, with a median survival of 9 years. Some 98% of tumours are non-Hodgkin lymphomas, usually the diffuse large B-cell subtype. Treatment is with combination chemotherapy and external beam radiotherapy.

Medullary carcinoma

This tumour arises from the parafollicular C cells of the thyroid. In addition to calcitonin, the tumour may secrete 5-hydroxytryptamine (5-HT, serotonin) and adrenocorticotrophic hormone (ACTH). Consequently, carcinoid syndrome (see Box 20.49) and Cushing syndrome (see p. 722) may occur. Medullary carcinoma of the thyroid occurs sporadically in 70%–90% cases; in 10%–30% there is a genetic predisposition that is inherited in an autosomal dominant fashion and due to an activating mutation in the *RET* gene. This inherited tendency normally forms part of one of the MEN syndromes (MEN 2a or 2b, p. 742) but, occasionally, susceptibility to medullary carcinoma is the only inherited trait (familial medullary thyroid cancer; this depends on the specific codon of the *RET* gene that is mutated).

Patients usually present in middle age with a firm thyroid mass. Cervical lymph node involvement is common but distant metastases are rare initially. Serum calcitonin levels are raised and are useful in monitoring response to treatment. Despite the very high levels of calcitonin found in some patients, hypocalcaemia is extremely rare; however, hypercalcitoninaemia can be associated with severe, watery diarrhoea.

Treatment is by total thyroidectomy with removal of regional cervical lymph nodes. Since the C cells do not trap iodine and are not responsive to TSH, there is no role for ^{131}I therapy or TSH suppression with levothyroxine. External beam radiotherapy may be considered in some patients at high risk of local recurrence. Vandetanib and cabozantinib are tyrosine kinase inhibitors licensed for patients with progressive advanced medullary cancer. Selpercatinib is also licensed in advanced disease for those with a *RET* mutation (either germline or somatic). The prognosis is not as good as papillary and follicular carcinoma, but individuals can live for many decades with persistent disease that behaves in an indolent fashion.

Riedel thyroiditis

Although not a form of thyroid cancer, the presentation is similar and differentiation can usually be made only by thyroid biopsy. It has an estimated incidence of 1 in 100 000. Riedel thyroiditis is an autoimmune disease and, in most cases, appears to be IgG4-related (p. 1074). Fibrosing variants of Hashimoto thyroiditis and Graves disease have also been described. There may be associated systemic features, e.g. mediastinal, retroperitoneal, salivary, and/or cardiovascular fibrosis, seen in around 30% of patients. Presentation is with a slow-growing goitre that is irregular and stony-hard. Tracheal and oesophageal compression occur often necessitating partial thyroidectomy. Other recognised local complications include recurrent laryngeal nerve palsy, hypoparathyroidism and eventually hypothyroidism. Immunosuppressive therapy may be indicated for symptomatic disease.

Congenital thyroid disease

Early treatment with levothyroxine is essential to prevent irreversible brain damage in children (cretinism) with congenital hypothyroidism. Routine screening of TSH levels in heel-prick blood samples obtained 5–7 days after birth (as part of the Guthrie test) shows congenital hypothyroidism has an incidence of approximately 1 in 3000. Causes include thyroid agenesis, ectopic or hypoplastic glands, and dyshormonogenesis. Levothyroxine replacement therapy should be initiated within 2 weeks

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of birth. Developmental assessment of infants treated at this early stage suggests an excellent response to treatment.

Dyshormonogenesis

Several genetic defects in thyroid hormone synthesis have been described; the most common results from deficiency of the intrathyroidal peroxidase enzyme. Homozygous individuals present with congenital hypothyroidism; heterozygotes present in the first two decades of life with goitre, normal thyroid hormone levels and a raised TSH. The combination of dyshormonogenetic goitre and nerve deafness is known as Pendred syndrome. Most cases of Pendred syndrome are caused by pathogenic variants in the *SLC26A4* gene, which encodes pendrin, the protein that transports iodide to the luminal surface of the follicular cell (see Fig. 20.3).

Thyroid hormone resistance

This is a rare disorder in which the pituitary and hypothalamus are resistant to feedback suppression of TSH by T3, sometimes due to pathogenic variants in the thyroid hormone receptor β gene or because of defects in deiodinase activity. TSH, T4 and T3, are all increased and patients may also have a goitre in adulthood. Thyroid hormone signalling is highly complex and involves different isozymes of both deiodinases and thyroid hormone receptors in different tissues. For this reason, some tissues do not share the resistance to thyroid hormone and there may be features of thyrotoxicosis (e.g. tachycardia). This condition can be difficult to distinguish from an equally rare TSH-producing pituitary tumour (TSHoma; see Box 20.5); administration of TRH tends to result in elevation of TSH in thyroid hormone resistance and not in TSHoma, but an MRI scan of the pituitary may be necessary to exclude an adenoma.

The reproductive system

Clinical practice in reproductive medicine is shared between several specialties, including gynaecology, urology, paediatric endocrinology, psychiatry and endocrinology. The following section is focused on disorders managed by adult endocrinologists.

Functional anatomy, physiology and investigations

The physiology of male and female reproductive function is illustrated in Figures 20.14 and 20.15, respectively. Pathways for synthesis of sex steroids are shown in Figure 20.20.

The male

In the male, the testis serves two principal functions: synthesis of testosterone by the interstitial Leydig cells under the control of luteinising hormone (LH), and spermatogenesis by Sertoli cells under the control of follicle-stimulating hormone (FSH) (but also requiring adequate testosterone). Negative feedback suppression of LH is mediated principally by testosterone, while secretion of another hormone produced by the testis, inhibin, suppresses FSH. The axis is optimally assessed by fasted, early morning measurement of testosterone, LH and FSH (as testosterone levels reach their peak in the morning and can be mildly suppressed post-prandially). Testosterone is largely bound in plasma to sex hormone-binding globulin and this can also be measure1d to determine the 'calculated free testosterone' or the 'bioavailable' testosterone. Testicular function can also be tested by semen analysis.

There is no equivalent of the menopause in men, although testosterone concentrations decline slowly from the fourth decade onwards.

The female

In the female, physiology varies during the normal menstrual cycle. FSH stimulates growth and development of ovarian follicles during the first 14 days after the menses. This leads to a gradual increase in oestradiol production from granulosa cells, which initially suppresses FSH secretion (negative feedback) but, once a threshold is reached, stimulates an increase in both the frequency and amplitude of gonadotrophin-releasing hormone (GnRH) pulses, resulting in a marked increase in LH secretion (positive feedback). The mid-cycle 'surge' of LH induces ovulation. After release of the ovum, the follicle differentiates into a corpus luteum, which secretes progesterone. Unless pregnancy occurs during the cycle, the corpus luteum regresses and the fall in progesterone levels results in menstrual bleeding. Circulating levels of oestrogen and progesterone in pre-menopausal women are, therefore, critically dependent on the time of the cycle. The most useful 'test' of ovarian function is a careful menstrual history: if menses are regular, measurement of gonadotrophins and oestrogen is not necessary. Ovulation can be confirmed by measuring plasma progesterone levels during the luteal phase ('day 21 progesterone').

Cessation of menstruation (the menopause) occurs at an average age of approximately 50 years in high-income countries. In the 5 years before, there is a gradual increase in the number of anovulatory cycles and this is referred to as the climacteric. Oestrogen and inhibin secretion falls and negative feedback results in increased pituitary secretion of LH and FSH (both typically to levels above 30 IU/L (3.3 μg/L)).

The pathophysiology of male and female reproductive dysfunction is summarised in Box 20.18.

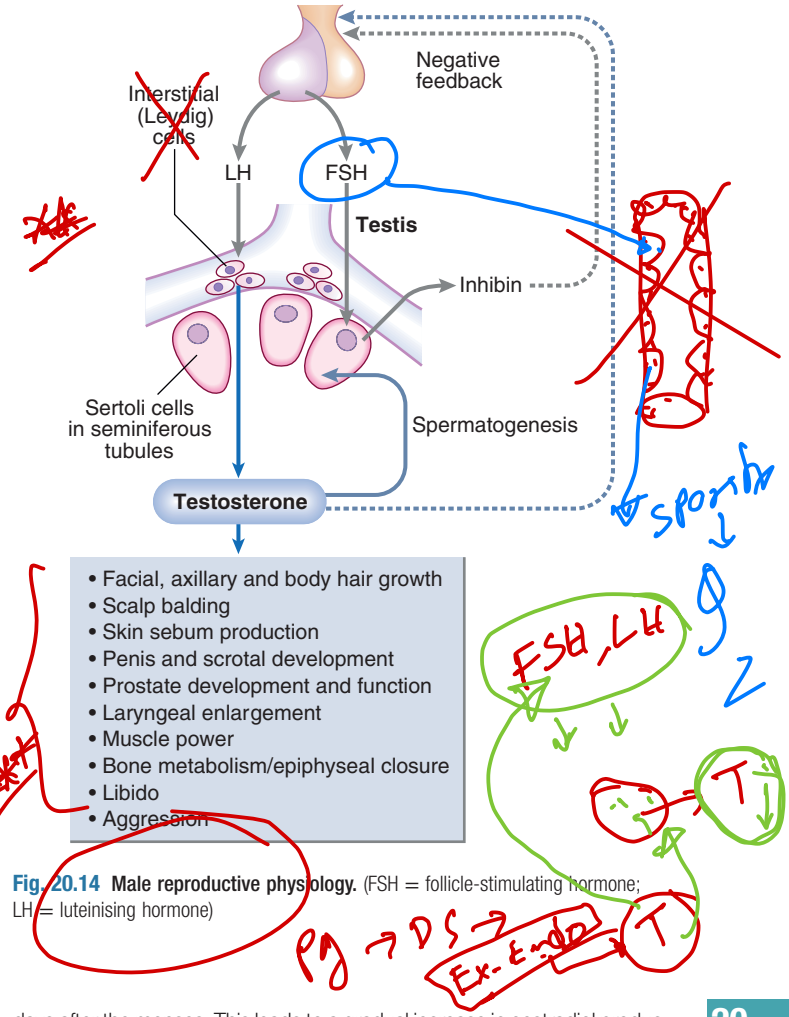

Fig. 20.14 Male reproductive physiology. (FSH = follicle-stimulating hormone; LH = luteinising hormone)

Presenting problems in reproductive disease

Delayed puberty

Normal pubertal development is discussed in Chapter 31. Puberty is considered to be delayed if the onset of the physical features of sexual maturation has not occurred by a chronological age that is 2.5 standard

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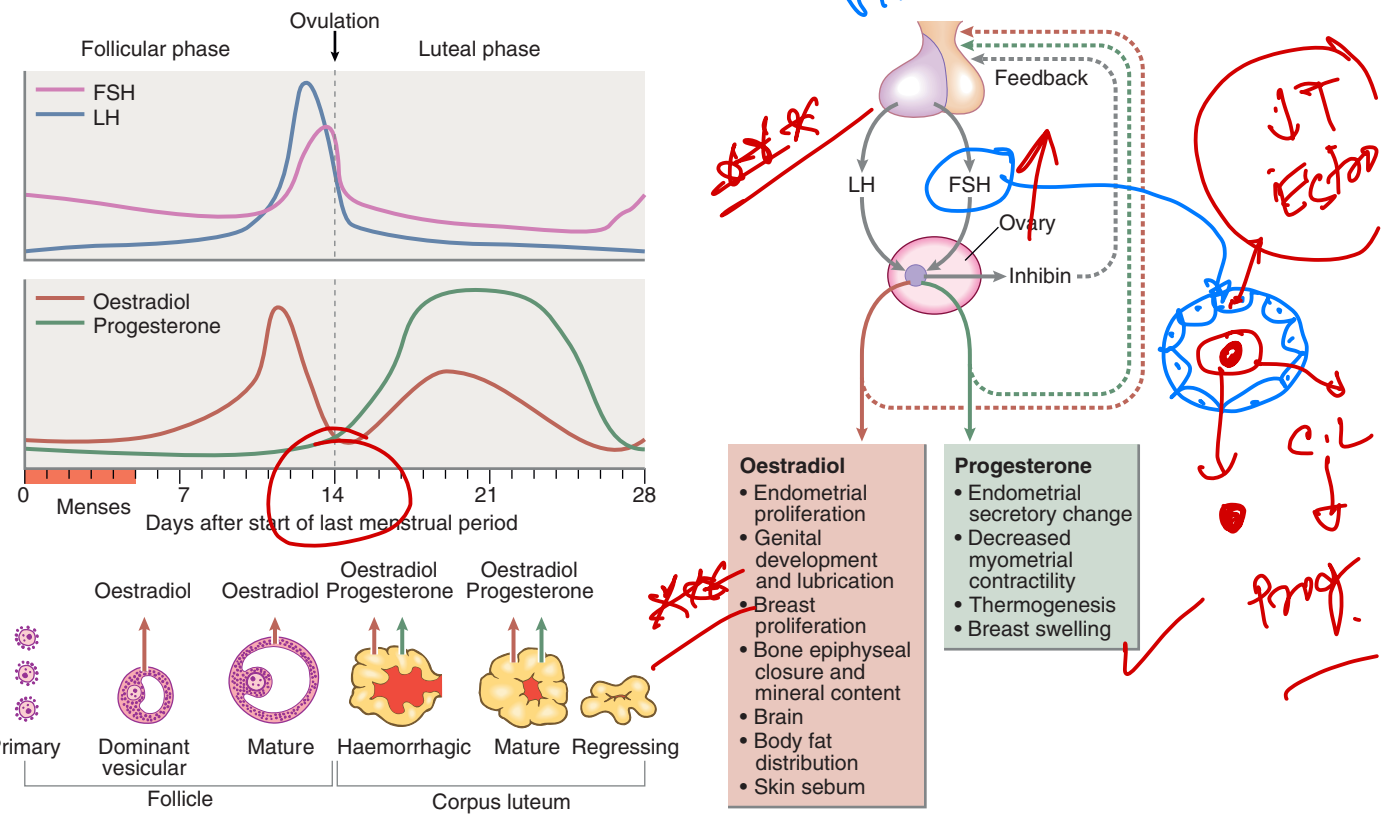

Fig. 20.15 **Female reproductive physiology and the normal menstrual cycle.** (FSH = follicle-stimulating hormone; LH = luteinising hormone)

20.18 Classification of diseases of the reproductive system

	Primary	Secondary
Hormone excess	Polycystic ovary syndrome Granulosa cell tumour Leydig cell tumour Teratoma	Pituitary gonadotrophinoma
Hormone deficiency	Hypogonadism (see Box 20.19) Turner syndrome Klinefelter syndrome	Hypopituitarism Isolated GnRH deficiency (Kallmann syndrome) Severe systemic illness, including anorexia nervosa
Hormone hypersensitivity	Idiopathic hirsutism	
Hormone resistance	Androgen resistance syndromes Complete ('testicular feminisation') Partial (Reifenstein syndrome) 5α-reductase type 2 deficiency	
Non-functioning tumours	Ovarian cysts Carcinoma Teratoma Seminoma	

(GnRH = gonadotrophin-releasing hormone)

20.19 Causes of delayed puberty and hypogonadism

Constitutional delay

Hypogonadotrophic hypogonadism

- Structural hypothalamic/pituitary disease (see Box 20.53)
- Functional gonadotrophin deficiency:
  - Chronic systemic illness (e.g. asthma, malabsorption, coeliac disease, cystic fibrosis, renal failure)
  - Opioid analgesia
  - Psychological stress
  - Anorexia nervosa
  - Excessive physical exercise
  - Hyperprolactinaemia
  - Other endocrine disease (e.g. Cushing syndrome, primary hypothyroidism)
- Isolated gonadotrophin deficiency (Kallmann syndrome)

Hypergonadotrophic hypogonadism

- Acquired gonadal damage:
  - Chemotherapy/radiotherapy to gonads
  - Trauma/surgery to gonads
  - Autoimmune gonadal failure
  - Mumps orchitis
  - Tuberculosis
  - Haemochromatosis
- Developmental/congenital gonadal disorders:
  - Steroid biosynthetic defects
  - Anorchidism/cryptorchidism in males
  - Klinefelter syndrome (47,XXY, male phenotype)
  - Turner syndrome (45,X, female phenotype)

deviations (SD) above the national average. In the UK, this is by the age of 14 in boys and 13 in girls. Genetic factors have a major influence in determining the timing of the onset of puberty, such that the age of menarche (the onset of menstruation) is often comparable within sibling and mother–daughter pairs and within ethnic groups. However, because there is also a threshold for body weight that acts as a trigger for normal puberty, the onset of puberty can be influenced by other factors, including nutritional status and chronic illness.

Clinical assessment

The differential diagnosis is shown in Box 20.19. The key issue is to determine whether the delay in puberty is simply because the 'clock

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20.20 Delayed puberty

- **Aetiology**: in boys the most common cause is constitutional delay, whereas in girls there is inevitably a structural hypothalamic/pituitary abnormality or a factor that affects their function.
- **Psychological effects**: whatever the underlying cause, delayed puberty is often associated with substantial psychological distress.
- **Investigations**: a karyotype should be performed in all adolescents with hypergonadotrophic hypogonadism, to exclude Turner and Klinefelter syndromes, unless there is an obvious precipitating cause.
- **Medical induction of puberty**: if this is being considered, it needs to be managed carefully and carried out in a controlled fashion, to avoid premature fusion of the epiphyses.

is running slow' (constitutional delay of puberty) or because there is pathology in the hypothalamus/pituitary (hypogonadotrophic hypogonadism) or the gonads (hypergonadotrophic hypogonadism). A general history and physical examination should be performed with particular reference to previous or current medical disorders, social circumstances and family history. Body proportions, sense of smell and pubertal stage should be carefully documented and, in boys, the presence or absence of testes in the scrotum noted. Current weight and height may be plotted on centile charts, along with parental heights. Previous growth measurements in childhood, which can usually be obtained from health records, are extremely useful. Healthy growth usually follows a centile. Usually, children with constitutional delay have always been small but have maintained a normal growth velocity that is appropriate for bone age. Poor linear growth, with 'crossing of the height centiles', is more likely to be associated with acquired disease. Issues that are commonly encountered in the management of adolescents with delayed puberty are summarised in Box 20.20.

Constitutional delay of puberty

This is the most common cause of delayed puberty, but is a much more frequent explanation for lack of pubertal development in boys than in girls. Affected children are healthy and have usually been more than 2 SD below the mean height for their age throughout childhood. There is often a history of delayed puberty in siblings or parents. Since sex steroids are essential for fusion of the epiphyses, 'bone age' can be estimated by X-rays of epiphyses, usually in the wrist and hand (see Fig 31.6; p. 1325); in constitutional delay, bone age is lower than chronological age. Constitutional delay of puberty should be considered as a normal variant, as puberty will commence spontaneously. However, affected children can experience significant psychological distress because of their lack of physical development, particularly when compared with their peers.

Hypogonadotrophic hypogonadism

This may be due to structural, inflammatory or infiltrative disorders of the pituitary and/or hypothalamus (see Box 20.53). In such circumstances, other pituitary hormones, such as growth hormone, are also likely to be deficient.

'Functional' gonadotrophin deficiency is caused by a variety of factors, including low body weight, chronic systemic illness (as a consequence of the disease itself or secondary malnutrition), endocrine disorders and profound psychosocial stress.

Isolated gonadotrophin deficiency is usually due to a genetic abnormality that affects the synthesis of either GnRH or gonadotrophins. The most common form is Kallmann syndrome, in which there is primary GnRH deficiency and, in most affected individuals, agenesis or hypoplasia of the olfactory bulbs, resulting in anosmia or hyposmia. If isolated gonadotrophin deficiency is left untreated, the epiphyses fail to fuse, resulting in tall stature with disproportionately long arms and legs relative to trunk height (eunuchoid habitus).

Cryptorchidism (undescended testes) and gynaecomastia are commonly observed in all forms of hypogonadotrophic hypogonadism.

Hypergonadotrophic hypogonadism

Hypergonadotrophic hypogonadism associated with delayed puberty is usually due to Klinefelter syndrome in boys and Turner syndrome in girls. Other causes of primary gonadal failure are shown in Box 20.19.

Investigations

Key measurements are LH and FSH, testosterone (in boys) and oestradiol (in girls). Chromosome analysis should be performed if gonadotrophin concentrations are elevated. If gonadotrophin concentrations are low, then the differential diagnosis lies between constitutional delay and hypogonadotrophic hypogonadism. A plain X-ray of the wrist and hand may be compared with a set of standard films to obtain a bone age. Full blood count, renal function, liver function, thyroid function and coeliac disease autoantibodies (see p. 837) should be measured, but further tests may be unnecessary if the blood tests are normal and the child has all the clinical features of constitutional delay. If hypogonadotrophic hypogonadism is suspected, neuroimaging and further investigations are required (see Box 20.51).

Management

Puberty can be induced using low doses of oral oestrogen in girls (e.g. ethinylestradiol 2 µg daily) or testosterone in boys (low doses of testosterone gel or depot testosterone esters). Higher doses carry a risk of early fusion of epiphyses. This therapy should be given in a specialist clinic where the progress of puberty and growth can be carefully monitored. In children with constitutional delay, this 'priming' therapy can be discontinued when endogenous puberty is established, usually in less than a year. In children with hypogonadism, the underlying cause should be treated and reversed if possible. If hypogonadism is permanent, sex hormone doses are gradually increased during puberty and full adult replacement doses given when development is complete.

Amenorrhoea

Primary amenorrhoea may be diagnosed in a female who has never menstruated; this usually occurs as a manifestation of delayed puberty but may also be a consequence of anatomical defects of the female reproductive system, such as endometrial hypoplasia or vaginal agenesis. Secondary amenorrhoea describes the cessation of menstruation in a female who has previously had periods. The causes of this common presentation are shown in Box 20.21. In non-pregnant women, secondary amenorrhoea is almost invariably a consequence of either ovarian or hypothalamic/pituitary dysfunction. Premature ovarian failure (premature menopause) is defined, arbitrarily, as occurring before 40 years of age. Rarely, endometrial adhesions (Asherman syndrome) can form after uterine curettage, surgery or infection with tuberculosis or schistosomiasis, preventing endometrial proliferation and shedding.

Clinical assessment

The underlying cause can often be suspected from associated clinical features and the patient's age. Hypothalamic/pituitary disease and premature ovarian failure result in oestrogen deficiency, which causes a variety of symptoms usually associated with the menopause (Box 20.22). A history of galactorrhoea should be sought. Significant weight loss of

20.21 Causes of secondary amenorrhoea

Physiological
- Pregnancy
- Menopause

Hypogonadotrophic hypogonadism (see Box 20.19)

Ovarian dysfunction
- Hypergonadotrophic hypogonadism (see Box 20.19)
- Polycystic ovary syndrome
- Androgen-secreting tumours

Uterine dysfunction
- Asherman syndrome

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20.22 Symptoms of oestrogen deficiency

Vasomotor effects	
• Hot flushes	• Sweating
Psychological	
• Anxiety • Irritability	• Emotional lability
Genitourinary	
• Dyspareunia • Urgency of micturition	• Vaginal infections

any cause can cause amenorrhoea by suppression of gonadotrophins. Weight gain may suggest hypothyroidism, Cushing syndrome (if other discriminatory features are present), or very rarely, a hypothalamic lesion. Hirsutism, obesity and long-standing irregular periods suggest polycystic ovary syndrome (PCOS). The presence of other autoimmune disease raises the possibility of autoimmune premature ovarian failure.

Investigations

Pregnancy should be excluded in women of reproductive age by measuring urine or serum human chorionic gonadotrophin (hCG). Serum LH, FSH, oestradiol, prolactin, testosterone, T4 and TSH should be measured and, in the absence of a menstrual cycle, can be taken at any time. Investigation of hyperprolactinaemia is described on page 738. High concentrations of LH and FSH with low or low-normal oestradiol suggest primary ovarian failure. Ovarian autoantibodies may be positive when there is an underlying autoimmune aetiology, and a karyotype should be performed in younger women to exclude mosaic Turner syndrome. Elevated LH, prolactin and testosterone levels, with normal oestradiol, are common in PCOS. Low levels of LH, FSH and oestradiol suggest hypothalamic or pituitary disease and a pituitary MRI is indicated.

There is some overlap in gonadotrophin and oestrogen concentrations between women with hypogonadotrophic hypogonadism and PCOS. If there is doubt as to the underlying cause of secondary amenorrhoea, then the response to 5–10 days of treatment with an oral progestogen (e.g. medroxyprogesterone acetate 5–10 mg daily) can be assessed. In women with PCOS, the progestogen will cause maturation of the (usually thickened) endometrium and menstruation will occur a few days after the progestogen is stopped. In women with hypogonadotrophic hypogonadism, menstruation does not occur following progestogen withdrawal because the endometrium is atrophic as a result of oestrogen deficiency. Transvaginal ultrasound can also be used to assess endometrial thickness and to examine the ovaries for evidence of polycystic change.

Assessment of bone mineral density by dual X-ray absorptiometry (DXA, see Ch. 25) may be appropriate in patients with low oestrogen levels.

Management

Where possible, the underlying cause should be treated. For example, women with functional amenorrhoea due to excessive exercise and low weight should be encouraged to reduce their exercise and regain some weight. The management of structural pituitary and hypothalamic disease is described on page 734 and that of PCOS on page 714.

In oestrogen-deficient women, replacement therapy may be necessary to treat symptoms and/or to prevent osteoporosis. Women who have had a hysterectomy can be treated with oestrogen alone but those with a uterus should be treated with combined oestrogen/progestogen therapy, since unopposed oestrogen increases the risk of endometrial cancer. Cyclical hormone replacement therapy (HRT) regimens typically involve giving oestrogen on days 1–21 and progestogen on days 14–21 of the cycle, and this can be conveniently administered as the oral contraceptive pill. If oestrogenic side-effects (fluid retention, hypertension and thrombosis) are a concern, then lower-dose oral or transdermal HRT may be more appropriate. Preparations that administer oestrogen and a progesterone continuously are available for women who do not wish to have a withdrawal bleed. A hormonal intrauterine device (a coil that slowly releases progestogen into the uterus and thus keeps the endometrium atrophic) is an alternative means of delivering the progestogen and may be used in combination with an oral or transdermal oestrogen (cyclical or continuous). There are some data to suggest that transdermal preparations (compared with oral) are associated with a lower risk of certain side-effects, such as venous thromboembolism.

The timing of the discontinuation of oestrogen replacement therapy is still a matter of debate. In post-menopausal women, HRT has been shown to relieve menopausal symptoms and to prevent osteoporotic fractures but is associated with adverse effects (such as an increased risk of breast cancer and venous thromboembolism), which are related to the duration of therapy and to the patient's age. In patients with premature menopause, HRT should be continued up to the age of around 50 years, but continued beyond this age only if there are continued symptoms of oestrogen deficiency on discontinuation.

Management of infertility in oestrogen-deficient women is described below.

Male hypogonadism

The clinical features of both hypo- and hypergonadotrophic hypogonadism include loss of libido, erectile dysfunction, lethargy with muscle weakness and decreased frequency of shaving. Patients may also present with gynaecomastia, infertility, delayed puberty, osteoporosis or anaemia. The causes of hypogonadism are listed in Box 20.19. Mild hypogonadism may also occur in older men, particularly in the context of central adiposity. Postulated mechanisms are complex and include reduction in GnRH and gonadotrophin secretion by cytokines or oestrogen released by adipose tissue. Testosterone levels also fall gradually with age in men (see Box 20.24) and this is associated with gonadotrophin levels that are low or inappropriately within the 'normal' range. There is an increasing trend to measure testosterone in older men, typically as part of an assessment of erectile dysfunction and reduced libido.

Investigations

Male hypogonadism is confirmed by demonstrating a low fasting 9 am serum testosterone level. The distinction between hypo- and hypergonadotrophic hypogonadism is by measurement of random LH and FSH. Patients with hypogonadotrophic hypogonadism should be investigated as described for pituitary disease on page 733. Pituitary imaging is not always necessary in biochemically mild testosterone deficiency (> 5 nmol/L), with otherwise normal pituitary function, in the context of obesity. Patients with hypergonadotrophic hypogonadism should have the testes examined for cryptorchidism or atrophy, and a karyotype should be performed (to identify Klinefelter syndrome).

Management

Testosterone replacement is clearly indicated in younger men with significant hypogonadism to prevent osteoporosis and to restore muscle power and libido. Debate exists as to whether replacement therapy is of benefit in mild hypogonadism associated with ageing and central adiposity, particularly in the absence of structural pituitary/hypothalamic disease or other pituitary hormone deficiency. In such instances, a therapeutic trial of testosterone therapy may be considered if symptoms are present (e.g. low libido and erectile dysfunction) and the serum testosterone is consistently low, but the benefits of therapy must be carefully weighed against the potential for harm (see below). Recent randomised controlled trial evidence has partially allayed concerns that testosterone replacement may increase cardiovascular risk in older men.

Routes of testosterone administration are shown in Box 20.23. First-pass hepatic metabolism of testosterone is highly efficient, so bioavailability of ingested preparations is poor. Doses of systemic testosterone can be titrated against symptoms; circulating testosterone levels may provide only a rough guide to dosage because they may be highly variable (see Box 20.23). Testosterone therapy can worsen prostatic hypertrophy and

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20.23 Options for androgen replacement therapy

Route of administration	Preparation	Dose	Frequency	Comments
Intramuscular	Testosterone undecanoate	1000 mg	Every 3 months	Smoother profile than testosterone enantate, with less frequent injections
	Testosterone enanthate	50–250 mg	Every 3–4 weeks	Produces peaks and troughs of testosterone levels that are outside the physiological range and may be symptomatic
Transdermal	Testosterone gel	Preparation dependent	Daily	Stable testosterone levels; transfer of gel can occur following skin-to-skin contact with another person

20.24 Gonadal function in old age

- **Post-menopausal osteoporosis**: a major public health issue due to the high incidence of associated fragility fractures, especially of hip.
- **Hormone replacement therapy**: should be prescribed only above the age of 50 for the short-term relief of symptoms of oestrogen deficiency.
- **Sexual activity**: many older people are sexually active.
- **'Male menopause'**: does not occur, although testosterone concentrations do fall with age. Testosterone therapy in mildly hypogonadal men may be of benefit for body composition, muscle and bone. A recent large randomised trial of testosterone replacement indicated no significant effect upon cardiovascular or prostatic disease.
- **Androgens in older women**: hirsutism and balding occur. In those rare patients with significantly elevated androgen levels, this may be pathological, e.g. from an ovarian tumour.

aggravate prostate carcinoma; prostate-specific antigen (PSA) should be measured before commencing testosterone therapy in men older than 50 years and monitored annually thereafter. Haemoglobin concentration should also be monitored, as androgen replacement can cause polycythaemia. Testosterone replacement inhibits spermatogenesis; treatment for fertility is described below.

Some important aspects of gonadal function in older women and men are summarised in Box 20.24.

Infertility

Infertility affects around 1 in 7 couples of reproductive age, often causing psychological distress. The main causes are listed in Box 20.25. In women, it may result from anovulation or abnormalities of the reproductive tract that prevent fertilisation or embryonic implantation, often damaged fallopian tubes from previous infection. In men, infertility may result from impaired sperm quality (e.g. reduced motility) or reduced sperm number. Azoospermia or oligospermia is usually idiopathic but may be a consequence of hypogonadism (see Box 20.19). Microdeletions of the Y chromosome are recognised as a cause of severely abnormal spermatogenesis. In many couples more than one factor causing subfertility is present, and in a large proportion no cause can be identified.

Clinical assessment

A history of previous pregnancies, relevant infections and surgery is important in both men and women. A sexual history must be explored sensitively, as some couples have intercourse infrequently or only when they consider the woman to be ovulating, and psychosexual difficulties are common. Irregular and/or infrequent menstrual periods are an indicator of anovulatory cycles in the woman, in which case causes such as PCOS should be considered. In men, the testes should be examined to confirm that both are in the scrotum and to identify any structural abnormality, such as small size, absent vas deferens or the presence of a varicocele.

Investigations

Investigations should generally be performed after a couple has failed to conceive despite unprotected intercourse for 12 months, unless there is an obvious abnormality like amenorrhoea. Both partners need to be investigated. The male partner needs a semen analysis to assess sperm count and quality. In women with regular periods, ovulation can be confirmed by an elevated serum progesterone concentration on day 21 of the menstrual cycle. Transvaginal ultrasound can be used to assess uterine and ovarian anatomy. Tubal patency may be examined at laparoscopy or by hysterosalpingography (HSG; a radio-opaque medium is injected into the uterus and should normally outline the fallopian tubes).

20.25 Causes of infertility

Female factors (35%–40%)

- Ovulatory dysfunction:
  - Polycystic ovary syndrome
  - Hypogonadotrophic hypogonadism (see Box 20.19)
  - Hypergonadotrophic hypogonadism (see Box 20.19)
- Tubular dysfunction:
  - Pelvic inflammatory disease (chlamydia, gonorrhoea)
  - Endometriosis
  - Previous sterilisation
  - Previous pelvic or abdominal surgery
- Cervical and/or uterine dysfunction:
  - Congenital abnormalities
  - Fibroids
  - Treatment for cervical carcinoma
  - Asherman syndrome

Male factors (35%–40%)

- Reduced sperm quality or production:
  - Y chromosome microdeletions
  - Varicocele
  - Hypergonadotrophic hypogonadism (see Box 20.19)
  - Hypogonadotrophic hypogonadism (see Box 20.19)
- Tubular dysfunction:
  - Varicocele
  - Congenital abnormality of vas deferens/epididymis
  - Previous sexually transmitted infection (chlamydia, gonorrhoea)
  - Previous vasectomy

Unexplained or mixed factors (20%–35%)

Management

Couples should be advised to have regular sexual intercourse, ideally every 2–3 days throughout the menstrual cycle. It is not uncommon for 'spontaneous' pregnancies to occur in couples undergoing investigations for infertility or with identified causes of male or female subfertility.

In women with anovulatory cycles secondary to PCOS, clomifene, which has partial anti-oestrogen action, blocks negative feedback of oestrogen on the hypothalamus/pituitary, causing gonadotrophin secretion and thus ovulation. In women with gonadotrophin deficiency or in whom anti-oestrogen therapy is unsuccessful, ovulation may be induced by direct stimulation of the ovary by daily injection of FSH and an injection of hCG or LH to induce follicular rupture at the appropriate time. In hypothalamic disease, pulsatile GnRH therapy with a portable infusion pump can be used to stimulate pituitary gonadotrophin secretion (note that non-pulsatile administration of GnRH or its analogues

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paradoxically suppresses LH and FSH secretion). Whatever method of ovulation induction is employed, monitoring of response is essential to avoid multiple ovulation. For clomifene, ultrasound monitoring is recommended for at least the first cycle. During gonadotrophin therapy, closer monitoring of follicular growth by transvaginal ultrasonography and blood oestradiol levels is mandatory. 'Ovarian hyperstimulation syndrome' is characterised by grossly enlarged ovaries and capillary leak with circulatory shock, pleural effusions and ascites. Anovulatory women who fail to respond to ovulation induction or who have primary ovarian failure may wish to consider using donated eggs or embryos, surrogacy and adoption.

Surgery to restore fallopian tube patency can be effective but in vitro fertilisation (IVF) is normally recommended. IVF is widely used for many causes of infertility and in unexplained cases of prolonged (>3 years) infertility. The success of IVF depends on age, with low success rates in women over 40 years.

Men with hypogonadotrophic hypogonadism who wish fertility are usually given injections of hCG several times a week (recombinant FSH may also be required in men with hypogonadism of pre-pubertal origin); it may take up to 2 years to achieve satisfactory sperm counts. Surgery is rarely an option in primary testicular disease but removal of a varicocele can improve semen quality. Extraction of sperm from the epididymis for IVF, and intracytoplasmic sperm injection (ICSI, when single spermatozoa are injected into each oocyte) are used in men with oligospermia or poor sperm quality who have primary testicular disease. Azoospermic men may opt to use donated sperm.

Gynaecomastia

Gynaecomastia is the presence of glandular breast tissue in males. Normal breast development in women is oestrogen-dependent, while androgens oppose this effect. Gynaecomastia results from an imbalance between androgen and oestrogen activity, which may reflect androgen deficiency or oestrogen excess. Causes are listed in Box 20.26. The most common are physiological: for example, in the newborn baby (due to maternal and placental oestrogens), in pubertal boys (in whom oestradiol concentrations reach adult levels before testosterone) and in older men (due to decreasing testosterone concentrations). Prolactin excess alone does not cause gynaecomastia.

Clinical assessment

A drug history is important. Gynaecomastia is often asymmetrical and palpation may allow breast tissue to be distinguished from the prominent adipose tissue (lipomastia) around the nipple that is often observed in obesity. Features of hypogonadism should be sought (see above) and the testes examined for evidence of cryptorchidism, atrophy or a tumour.

20.26 Causes of gynaecomastia

Idiopathic

Physiological

Drug-induced

- Cimetidine
- Digoxin
- Anti-androgens (cyproterone acetate, spironolactone)
- Some exogenous anabolic steroids (diethylstilbestrol)
- Cannabis

Hypogonadism (see Box 20.19)

Androgen resistance syndromes

Oestrogen excess

- Liver failure (impaired steroid metabolism)
- Oestrogen-secreting tumour (e.g. of testis)
- Human chorionic gonadotrophin-secreting tumour (e.g. of testis or lung)

Investigations

If a clinical distinction between gynaecomastia and adipose tissue cannot be made, then ultrasonography or mammography is required. A random blood sample should be taken for testosterone, LH, FSH, oestradiol, prolactin and hCG. Elevated oestrogen concentrations are found in testicular tumours and hCG-producing neoplasms.

Management

An adolescent with gynaecomastia who is progressing normally through puberty may be reassured that the gynaecomastia will usually resolve once development is complete. If puberty does not proceed normally, then there may be an underlying abnormality that requires investigation. Gynaecomastia may cause significant psychological distress, especially in adolescent boys, and surgical excision may be justified for cosmetic reasons. There is little evidence to suggest testosterone replacement therapy ameliorates gynaecomastia in hypogonadal men and any other identifiable underlying cause should be addressed if possible. The anti-oestrogen tamoxifen may be effective in reducing the size of the breast tissue.

Hirsutism

Hirsutism refers to the excessive growth of terminal hair (the thick, pigmented hair usually associated with the adult male chest) in an androgen-dependent distribution in women (upper lip, chin, chest, back, lower abdomen, thigh, forearm) and is one of the most common presentations of endocrine disease. It should be distinguished from hypertrichosis, which is generalised excessive growth of vellus hair (the thin, non-pigmented hair that is typically found all over the body from childhood onwards). The aetiology of androgen excess is shown in Box 20.27.

Clinical assessment

The severity of hirsutism is subjective. Some women suffer profound embarrassment from a degree of hair growth that others would not consider remarkable. Important observations are a drug and menstrual history, calculation of body mass index, measurement of blood pressure and examination for virilisation (clitoromegaly, deep voice, male-pattern balding, breast atrophy) and associated features, including acne vulgaris or Cushing syndrome. Hirsutism of recent onset associated with virilisation is suggestive of an androgen-secreting tumour or ovarian hyperthecosis.

Investigations

A random blood sample should be taken for testosterone, prolactin, LH and FSH. If there are clinical features of Cushing syndrome, further investigations should be performed as detailed on page 722.

If testosterone levels are more than twice the upper limit of normal for females, idiopathic hirsutism and PCOS are less likely, especially if LH and FSH levels are low. Under these circumstances, other causes of androgen excess should be sought. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency is diagnosed by an ACTH stimulation test with measurement of 17-OH-progesterone. In post-menopausal women with significant hyperandrogenism, administration of GnRH analogue can be helpful in differentiating between an ovarian (>50% suppression of testosterone) or adrenal source (≤50% suppression) of androgen excess. The tumour should then be sought by CT or MRI of the adrenals and ovaries, as indicated by biochemical testing.

Management

This depends on the cause (Box 20.27). Options for the treatment of PCOS and idiopathic hirsutism are similar and are described below.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) affects up to 10% of women of reproductive age. It is a heterogeneous disorder (Box 20.28), often associated with obesity, for which the primary cause remains uncertain.

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20.27 Causes of hirsutism

Cause	Clinical features	Investigation findings	Treatment
Idiopathic	Often familial Mediterranean or Asian background	Normal	Cosmetic measures Anti-androgens
Polycystic ovary syndrome	Obesity Oligomenorrhoea or secondary amenorrhoea Infertility	LH:FSH ratio > 2.5:1 Minor elevation of androgens* Mild hyperprolactinaemia	Weight loss Cosmetic measures Anti-androgens (Metformin, glitazones may be useful)
Congenital adrenal hyperplasia (95% 21-hydroxylase deficiency)	Pigmentation History of salt-wasting in childhood, ambiguous genitalia, or adrenal crisis when stressed	Elevated androgens* that suppress with dexamethasone Abnormal rise in 17-OH-progesterone with ACTH	Glucocorticoid replacement administered in reverse rhythm to suppress early morning ACTH
Exogenous androgen administration	Athletes Virilisation	Low LH and FSH Analysis of urinary androgens may detect drug of misuse	Stop steroid misuse
Androgen-secreting tumour of ovary or adrenal cortex	Rapid onset Virilisation: clitoromegaly, deep voice, balding, breast atrophy	High androgens* that do not suppress with GnRH analogues Low LH and FSH CT or MRI usually demonstrates a tumour	Surgical excision
Cushing syndrome	Clinical features of Cushing syndrome	Normal or mild elevation of adrenal androgens* See investigations (p. 721)	Treat the cause

*e.g. Serum testosterone levels in women: < 2 nmol/L (< 58 ng/dL) is normal; 2–5 nmol/L (58–144 ng/dL) is minor elevation; > 5 nmol/L (> 144 ng/dL) is high and requires further investigation.
(ACTH = adrenocorticotrophic hormone; CT = computed tomography; FH = follicle-stimulating hormone; GnRH = gonadotrophin releasing hormone; LH = luteinising hormone; MRI = magnetic resonance imaging)

20.28 Features of polycystic ovary syndrome

Mechanisms*	Manifestations
Pituitary dysfunction	High serum LH High serum prolactin
Anovulatory menstrual cycles	Oligomenorrhoea Secondary amenorrhoea Cystic ovaries Infertility
Androgen excess	Hirsutism Acne
Obesity	Hyperglycaemia Elevated oestrogens
Insulin resistance	Dyslipidaemia Hypertension

*These mechanisms are interrelated; it is not known which, if any, is primary. PCOS probably represents the common endpoint of several different pathologies.
(LH = luteinising hormone)

Genetic factors probably play a role, since PCOS often affects several family members. The severity and clinical features of PCOS vary markedly between individual patients but diagnosis is usually made during the investigation of hirsutism or amenorrhoea/oligomenorrhoea. Infertility may also be present. There is no universally accepted definition but it has been recommended that a diagnosis of PCOS requires the presence of two of the following three features:

- menstrual irregularity
- clinical or biochemical androgen excess
- multiple cysts in the ovaries (most readily detected by transvaginal ultrasound; Fig. 20.16).

Women with PCOS are at increased risk of glucose intolerance and some authorities recommend screening for type 2 diabetes and other cardiovascular risk factors associated with the metabolic syndrome.

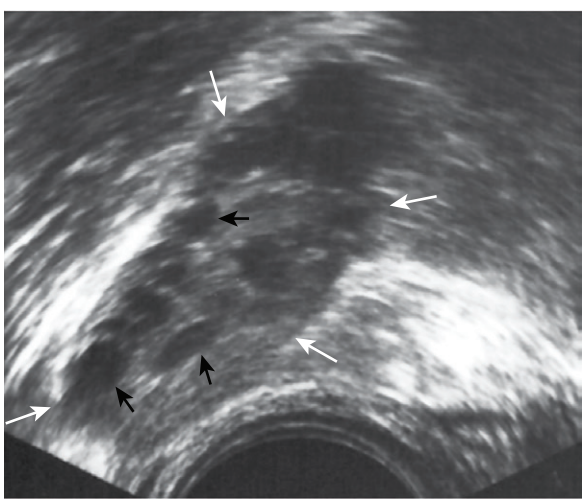

Fig. 20.16 Polycystic ovary. A transvaginal ultrasound scan showing multiple cysts (some indicated by black arrows) in the ovary (highlighted by white arrows) of a woman with polycystic ovary syndrome.

Management

This should be directed at the presenting complaint but all women with PCOS who are overweight should be encouraged to lose weight, as this can improve several symptoms, including menstrual irregularity, and reduces the risk of type 2 diabetes.

Menstrual irregularity and infertility

Most women with PCOS have oligomenorrhoea, with irregular, heavy menstrual periods. This may not require treatment unless fertility is desired. Metformin may restore regular ovulatory cycles in overweight women by reducing insulin resistance, although it is less effective than clomifene at restoring fertility as measured by successful pregnancy.

In women who have very few periods each year or are amenorrhoeic, the high oestrogen concentrations associated with PCOS can cause

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endometrial hyperplasia. Progestogens can be administered on a cyclical basis to induce regular shedding of the endometrium and a withdrawal bleed, or a progestogen-impregnated intrauterine coil can be fitted.

Hirsutism

For hirsutism, most patients will have used cosmetic measures, such as shaving, bleaching and waxing, before consulting a doctor. Electrolysis and laser treatment are effective for small areas like the upper lip and for chest hair but are expensive. Eflornithine cream inhibits ornithine decarboxylase in hair follicles and may reduce hair growth when applied daily to affected areas of the face.

If conservative measures are unsuccessful, anti-androgen therapy is given (Box 20.29). The life cycle of a hair follicle is at least 3 months and no improvement is likely before this time, when follicles have shed their hair and replacement hair growth has been suppressed. Metformin is less effective at treating hirsutism than at restoring menstrual regularity. Unless weight is lost, hirsutism will return if therapy is discontinued. The patient should know that prolonged exposure to some agents may not be desirable and they should be stopped before pregnancy.

Turner syndrome

Turner syndrome affects around 1 in 2500 females. It is classically associated with a 45,X karyotype but other cytogenetic abnormalities may be responsible, including mosaic forms (e.g. 45,X/46,XX or 45,X/46,XY) and partial deletions of an X chromosome.

Clinical features

These are shown in Figure 20.17.

Individuals with Turner syndrome invariably have short stature from an early age and this is often the initial presenting symptom; it is probably due to haploinsufficiency of the *SHOX* gene, one copy of which is found

i 20.29 Anti-androgen therapy

Mechanism of action	Drug	Dose	Hazards
Androgen receptor antagonism	Spironolactone	25–200 mg daily	Electrolyte disturbance
5α-reductase inhibition (prevent conversion of testosterone to active dihydrotestosterone)	Finasteride	5 mg daily	Limited clinical experience; possibly less efficacious than other treatments
Suppression of ovarian steroid production and elevation of sex hormone-binding globulin	Oestrogen	As co-cyprindiol, a combination with low-dose cyproterone acetate (androgen receptor antagonist) *or* Conventional oestrogen-containing contraceptive	Venous thromboembolism Hypertension Hepatic dysfunction Hepatic neoplasms (rare) Weight gain Dyslipidaemia Increased breast and endometrial carcinoma

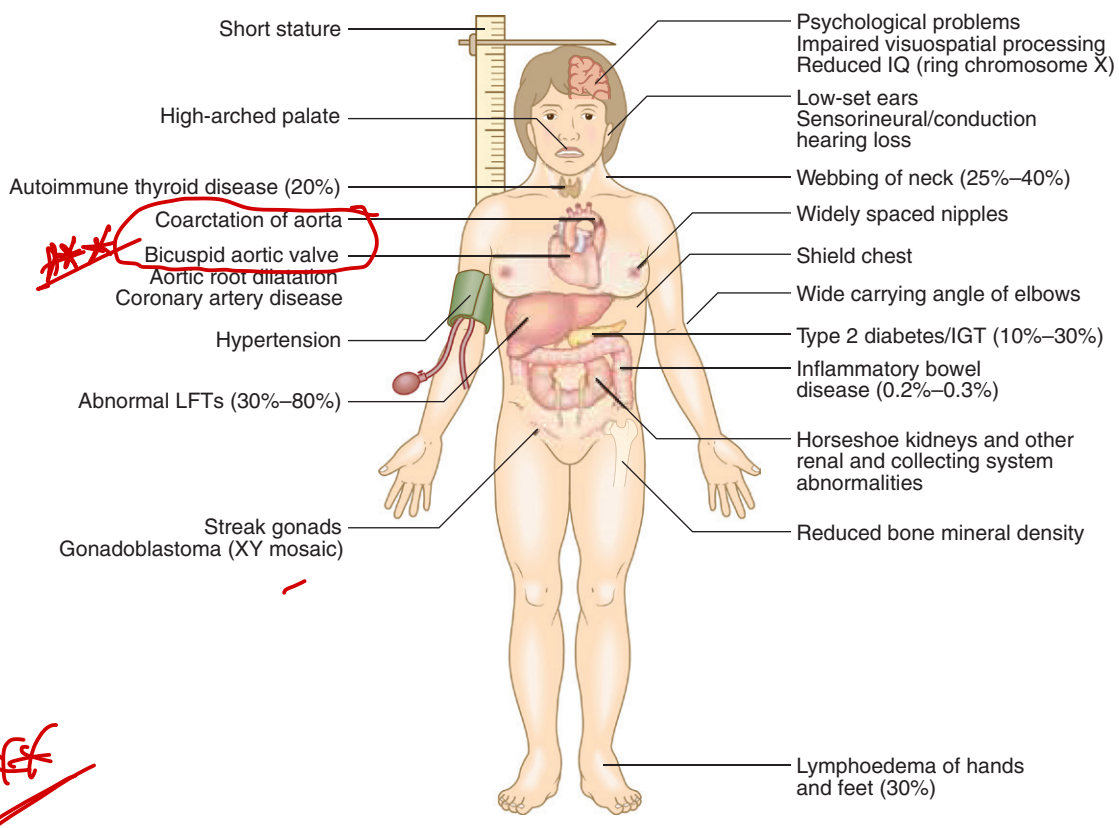

Fig. 20.17 Clinical features of Turner syndrome (45,X). (IGT = impaired glucose tolerance; LFTs = liver function tests)

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on both the X and Y chromosomes, which encodes a protein that is predominantly found in bone fibroblasts.

The genital tract and external genitalia in Turner syndrome are female in character, since this is the default developmental outcome in the absence of testes. Ovarian tissue develops normally until the third month of gestation, but thereafter there is gonadal dysgenesis with accelerated degeneration of oöcytes and increased ovarian stromal fibrosis, resulting in 'streak ovaries'. The inability of ovarian tissue to produce oestrogen results in loss of negative feedback and elevation of FSH and LH concentrations.

There is a wide variation in the spectrum of associated somatic abnormalities. The severity of the phenotype is, in part, related to the underlying cytogenetic abnormality. Mosaic individuals may have only mild short stature and may enter puberty spontaneously before developing gonadal failure.

Diagnosis and management

The diagnosis of Turner syndrome can be confirmed by karyotype analysis. Short stature, although not directly due to growth hormone deficiency, responds to high doses of growth hormone. Prophylactic gonadectomy is recommended for individuals with 45,X/46,XY mosaicism because there is an increased risk of gonadoblastoma. Pubertal development can be induced with oestrogen therapy but causes fusion of the epiphyses and cessation of growth. The timing of pubertal induction therefore needs to be carefully planned. Adults with Turner syndrome require long-term oestrogen replacement therapy and should be monitored periodically for the development of aortic root dilatation, hearing loss and other somatic complications.

Klinefelter syndrome

Klinefelter syndrome affects approximately 1 in 1000 males and is usually associated with a 47,XXY karyotype. However, other cytogenetic variants may be responsible, especially 46,XY/47,XXY mosaicism. The principal pathological abnormality is dysgenesis of the seminiferous tubules. This is evident from infancy (and possibly even in utero) and progresses with age. By adolescence, hyalinisation and fibrosis are present within the seminiferous tubules and Leydig cell function is impaired, resulting in hypogonadism.

Clinical features

The diagnosis is typically made in adolescents who have presented with gynaecomastia and failure to progress normally through puberty. Affected individuals usually have small, firm testes. Tall stature is apparent from early childhood, reflecting characteristically long leg length associated with 47,XXY, and may be exacerbated by androgen deficiency with lack of epiphyseal closure in puberty. Other clinical features may include learning difficulties and behavioural disorders, as well as an increased risk of breast cancer and type 2 diabetes in later life. The spectrum of clinical features is wide and some individuals, especially those with 46,XY/47,XXY mosaicism, may pass through puberty normally and be identified only during investigation for infertility.

Diagnosis and management

Klinefelter syndrome is suggested by the typical phenotype in a patient with hypergonadotrophic hypogonadism and can be confirmed by karyotype analysis. Individuals with clinical and biochemical evidence of androgen deficiency require androgen replacement (see Box 20.23). Although success rates are variable, pregnancy can occur following ICSI therapy where sperm has been surgically retrieved from the gonads of men with Klinefelter syndrome.

The parathyroid glands

Parathyroid hormone (PTH) plays a key role in the regulation of calcium and phosphate homeostasis and vitamin D metabolism, as shown in Figure 25.60. The consequences of altered function of this axis in gut and renal disease are covered in Chapters 22 and 18, respectively. Other metabolic bone diseases are explored in Chapter 25. Here, the investigation of hypercalcaemia and hypocalcaemia and disorders of the parathyroid glands are discussed.

Functional anatomy, physiology and investigations

The four parathyroid glands lie behind the lobes of the thyroid. The parathyroid chief cells respond directly to changes in calcium concentrations via a G protein-coupled cell surface receptor (the calcium-sensing receptor) located on the cell surface (see Fig. 25.60). When serum ionised calcium levels fall, PTH secretion rises. PTH is a single-chain polypeptide of 84 amino acids. It acts on the renal tubules to promote reabsorption of calcium and reduce reabsorption of phosphate, and on the skeleton to increase osteoclastic bone resorption and bone formation. PTH also promotes the conversion of 25-hydroxyvitamin D to the active metabolite, 1,25-dihydroxyvitamin D; the 1,25-dihydroxyvitamin D, in turn, enhances calcium absorption from the gut.

More than 99% of total body calcium is in bone. Prolonged exposure of bone to high levels of PTH is associated with increased osteoclastic activity and new bone formation, but the net effect is to cause bone loss with mobilisation of calcium into the extracellular fluid. In contrast, pulsatile release of PTH causes net bone gain. This effect is exploited therapeutically in the treatment of osteoporosis, as discussed in Chapter 25.

The differential diagnosis of disorders of calcium metabolism requires measurement of calcium phosphate, alkaline phosphatase, renal function, PTH and 25-hydroxyvitamin D. Although the parathyroid glands detect and respond to ionised calcium levels, most clinical laboratories measure only total serum calcium levels. About 50% of total calcium is bound to organic ions, such as citrate or phosphate, and to proteins, especially albumin. Accordingly, if the serum albumin level is reduced, total calcium concentrations should be 'corrected' by adjusting the value for calcium upwards by 0.02 mmol/L (0.08 mg/dL) for each 1 g/L reduction in albumin below 40 g/L. If albumin concentrations are significantly low, as in severe acute illness and other chronic illness such as liver cirrhosis, this correction is less accurate and measurement of ionised calcium is recommended.

Calcitonin is secreted from the parafollicular C cells of the thyroid gland. Although it is a useful tumour marker in medullary carcinoma of thyroid, its release from the thyroid is of no clinical relevance to calcium homeostasis in humans.

Disorders of the parathyroid glands are summarised in Box 20.30. Some specific features of parathyroid disease in older people are summarised in Box 20.31.

Presenting problems in parathyroid disease

Hypercalcaemia

Hypercalcaemia is one of the most common biochemical abnormalities and is often detected during routine biochemical analysis in asymptomatic patients. However, it can present with chronic symptoms, as described below, and occasionally as an acute emergency with severe hypercalcaemia and dehydration.

Causes of hypercalcaemia are listed in Box 20.32. Of these, primary hyperparathyroidism and malignant hypercalcaemia are by far the most common. Familial hypocalciuric hypercalcaemia (FHH) is a rare but important cause that needs differentiation from primary hyperparathyroidism (HPT). Lithium may cause hyperparathyroidism by reducing the sensitivity of the calcium-sensing receptor.

Clinical assessment

Symptoms and signs of hypercalcaemia include polyuria and polydipsia, renal colic, lethargy, anorexia, nausea, dyspepsia and peptic ulceration, constipation, depression, drowsiness and impaired cognition. Patients

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20.30 Classification of diseases of the parathyroid glands

	Primary	Secondary
Hormone excess	Primary hyperparathyroidism Parathyroid adenoma Parathyroid carcinoma[1] Parathyroid hyperplasia[2] Tertiary hyperparathyroidism (following prolonged secondary hyperparathyroidism)	Secondary hyperparathyroidism Chronic kidney disease Malabsorption Vitamin D deficiency
Hormone deficiency	Hypoparathyroidism Post-surgical Autoimmune Inherited	
Hormone hypersensitivity	Autosomal dominant hypercalciuric hypocalcaemic (CASR-activating mutation)	
Hormone resistance	Pseudohypoparathyroidism Familial hypocalciuric hypercalcaemia	
Non-functioning tumours	Parathyroid carcinoma[1]	

[1]Parathyroid carcinomas may or may not produce parathyroid hormone.
[2]In multiple endocrine neoplasia (MEN) syndromes (p. 742).
(CASR = calcium-sensing receptor)

20.31 The parathyroid glands in old age

- **Osteoporosis**: always exclude osteomalacia and hyperparathyroidism by checking vitamin D and calcium concentrations.
- **Primary hyperparathyroidism**: more common with ageing. Older people can often be observed without surgical intervention.
- **Hypercalcaemia**: may cause delirium.
- **Vitamin D deficiency**: common because of limited exposure to the sun and reduced ability of older skin to synthesise cholecalciferol.

20.32 Causes of hypercalcaemia

With normal or elevated parathyroid hormone (PTH) levels

- Primary or tertiary hyperparathyroidism
- Lithium-induced hyperparathyroidism
- Familial hypocalciuric hypercalcaemia

With low PTH levels

- Malignancy (lung, breast, myeloma, renal, lymphoma, thyroid)
- Elevated 1,25-dihydroxyvitamin D (vitamin D intoxication, sarcoidosis, human immunodeficiency virus, other granulomatous disease)
- Thyrotoxicosis
- Paget disease with immobilisation
- Milk-alkali syndrome
- Thiazide diuretics
- Glucocorticoid deficiency

with malignant hypercalcaemia can have a rapid onset of symptoms and may have clinical features that help to localise the tumour.

The classic symptoms of primary hyperparathyroidism are described by the adage 'bones, stones and abdominal groans', but few patients present in this way nowadays and the disorder is most often picked up as an incidental finding on biochemical testing. About 50% of patients with primary hyperparathyroidism are asymptomatic while others have non-specific symptoms such as polyuria, thirst, fatigue, depression and generalised aches and pains. Some present with renal calculi and it has been estimated that 5% of first stone formers and 15% of recurrent stone formers have primary hyperparathyroidism. Hypertension is a common association with hyperparathyroidism. Parathyroid tumours are almost never palpable.

A family history of hypercalcaemia raises the possibility of FHH or MEN.

Investigations

The most discriminatory investigation is measurement of PTH. If PTH levels are elevated (or less commonly 'inappropriately' in the upper half of the normal range) in the presence of hypercalcaemia, then primary hyperparathyroidism is the most likely diagnosis. High plasma phosphate and alkaline phosphatase accompanied by renal impairment suggest tertiary hyperparathyroidism. Hypercalcaemia may cause nephrocalcinosis and renal tubular impairment, resulting in hyperuricaemia and hyperchloraemia.

Patients with FHH can present with a similar biochemical picture to primary hyperparathyroidism but typically have low urinary calcium excretion (a ratio of urinary calcium clearance to creatinine clearance of < 0.01). The diagnosis of FHH can be confirmed by screening family members for hypercalcaemia and/or identifying a genetic cause (most commonly an inactivating variant in *CASR*, the gene encoding the calcium-sensing receptor). FHH is much less common than primary hyperparathyroidism.

If PTH is low and no other cause is apparent, then malignancy with or without bony metastases is likely. PTH-related peptide, which is often responsible for the hypercalcaemia associated with malignancy, is not detected by PTH assays, but can be measured by a specific assay (although this is not usually necessary). Unless the source is obvious, the patient should be screened for malignancy with a chest X-ray, myeloma screen (see p. 1000) and CT as appropriate.

Management

Treatment of severe hypercalcaemia and primary hyperparathyroidism is described below and on page 171. FHH does not require any specific intervention.

Hypocalcaemia

Aetiology

Hypocalcaemia is much less common than hypercalcaemia. The differential diagnosis is shown in Box 20.33. The most common cause of a low total serum calcium is a low serum albumin with normal ionised calcium concentration. Conversely, ionised calcium may be low in the face of normal total serum calcium in patients with alkalosis: for example, as a result of hyperventilation.

Hypocalcaemia may also develop as a result of magnesium depletion and should be considered in patients with malabsorption, those on diuretic or proton pump inhibitor therapy, and/or those with a history of alcohol excess. Magnesium deficiency causes hypocalcaemia by impairing the ability of the parathyroid glands to secrete PTH (resulting in PTH

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20.33 Differential diagnosis of hypocalcaemia

	Total serum calcium	Ionised serum calcium	Serum phosphate	Serum PTH	Comments
Hypoalbuminaemia	↓	↔	↔	↔	Adjust calcium upwards by 0.02 mmol/L (0.08 mg/dL) for every 1 g/L reduction in albumin below 40 g/L
Alkalosis	↔	↓	↔	↔ or ↑	p. 675
Vitamin D deficiency	↓	↓	↓	↑	p. 1081
Chronic renal failure	↓	↓	↑	↑	Due to impaired vitamin D hydroxylation Serum creatinine ↑
Hypoparathyroidism	↓	↓	↑	↓	See text
Pseudohypoparathyroidism	↓	↓	↑	↑	Characteristic phenotype (see text)
Acute pancreatitis	↓	↓	↔ or ↓	↑	Usually clinically obvious Serum amylase and/or lipase ↑
Hypomagnesaemia	↓	↓	Variable	↓ or ↔	Treatment of hypomagnesaemia may correct hypocalcaemia

(↑ = levels increased; ↓ = levels reduced; ↔ = levels normal)

concentrations that are low or inappropriately in the reference range) and may also impair the actions of PTH on bone and kidney.

Clinical assessment

Mild hypocalcaemia is often asymptomatic but, with more profound reductions in serum calcium, tetany can occur. This is characterised by muscle spasms due to increased excitability of peripheral nerves.

Children are more liable to develop tetany than adults and present with a characteristic triad of carpopedal spasm, stridor and convulsions, although one or more of these may be found independently of the others. In carpopedal spasm, the hands adopt a characteristic position with flexion of the metacarpophalangeal joints of the fingers and adduction of the thumb ('main d'accoucheur'). Pedal spasm can also occur but is less frequent. Stridor is caused by spasm of the glottis. Adults can also develop carpopedal spasm in association with tingling of the hands and feet and around the mouth, but stridor and fits are rare.

Latent tetany may be detected by eliciting the Trousseau sign: inflation of a sphygmomanometer cuff on the upper arm to more than the systolic blood pressure is followed by carpal spasm within 3 minutes. Less specific is the Chvostek sign, in which tapping over the branches of the facial nerve as they emerge from the parotid gland produces twitching of the facial muscles.

Hypocalcaemia can cause papilloedema and prolongation of the ECG QT interval, which may predispose to ventricular arrhythmias. Prolonged hypocalcaemia and hyperphosphataemia (as in hypoparathyroidism) may cause calcification of the basal ganglia, grand mal epilepsy, psychosis and cataracts. Hypocalcaemia associated with hypophosphataemia, as in vitamin D deficiency, causes rickets in children and osteomalacia in adults.

Management

Emergency management of hypocalcaemia associated with tetany is given in Box 20.34. Treatment of chronic hypocalcaemia is described on page 1081.

20.34 Management of severe hypocalcaemia

Immediate management

- 10–20 mL 10% calcium gluconate IV over 10–20 mins
- Continuous IV infusion may be required for several hours (equivalent of 10 mL 10% calcium gluconate/hr)
- Cardiac monitoring is recommended

If associated with hypomagnesaemia

- 24 mmol (6 g) magnesium sulphate in 500 mL 0.9% sodium chloride or 5% dextrose IV over 24 hours
- Most parenteral magnesium will be excreted in the urine, so further doses may be required to replenish body stores

(IV = intravenous)

Primary hyperparathyroidism

Primary hyperparathyroidism is caused by autonomous secretion of PTH, usually by a single parathyroid adenoma. It should be distinguished from secondary hyperparathyroidism, in which there is a physiological increase in PTH secretion to compensate for prolonged hypocalcaemia (plasma calcium levels are not elevated in secondary hyperparathyroidism); and from tertiary hyperparathyroidism, in which continuous stimulation of the parathyroids over a prolonged period of time results in adenoma formation and autonomous PTH secretion (Box 20.35). This is most commonly seen in individuals with advanced chronic kidney disease.

20.35 Hyperparathyroidism

Type	Serum calcium	PTH
Primary Single adenoma (90%) Multiple adenomas (4%) Nodular hyperplasia (5%) Carcinoma (1%)	Raised	Not suppressed
Secondary Chronic renal failure Malabsorption Osteomalacia and rickets	Low	Raised
Tertiary	Raised	Not suppressed

The prevalence of primary hyperparathyroidism is about 1 in 500 and it is 2–3 times more common in women than men; 90% of patients are over 50 years of age. It also occurs in the familial MEN syndromes, in which case hyperplasia or multiple adenomas of all four parathyroid glands are more likely than a solitary adenoma. Primary hyperparathyroidism can also be caused by parathyroid carcinoma, although this accounts for less than 1% of cases. The presence of parathyroid carcinoma should prompt assessment for pathogenic variants of *CDC73*, which are associated with hyperparathyroidism–jaw tumour syndrome (primary hyperparathyroidism and ossifying fibromas of the jaw).

Clinical and radiological features

The clinical presentation of primary hyperparathyroidism is described on page 717. Parathyroid bone disease is now extremely rare due to earlier diagnosis and treatment, and plain X-ray assessment is not routinely recommended. Osteitis fibrosa results from increased bone resorption

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by osteoclasts with fibrous replacement in the lacunae. This may present as bone pain and tenderness, fracture and deformity. Chondrocalcinosis can occur due to deposition of calcium pyrophosphate crystals within articular cartilage. It typically affects the menisci at the knees and can result in secondary degenerative arthritis or predispose to attacks of acute pseudogout (p. 1047). Skeletal X-rays are usually normal in mild primary hyperparathyroidism but DXA (including assessment of forearm bone mineral density) should be obtained as a matter of routine in people with primary hyperparathyroidism to exclude osteoporosis (a potential indication for surgical intervention). Renal imaging (ultrasound, plain X-ray or CT of kidneys, ureters and bladder (CT KUB)) is recommended to screen for asymptomatic nephrocalcinosis or nephrolithiasis.

Investigations

The diagnosis can be confirmed by finding a raised (or inappropriately normal) PTH level in the presence of hypercalcaemia, provided that FHH is excluded. Parathyroid scanning by ultrasound examination is often sufficient to localise an adenoma prior to surgery, although it is highly dependent on an experienced operator. Where ultrasound is equivocal, or does not identify an adenoma, a range of additional imaging modalities are available. These include ^{99m}Tc sestamibi scintigraphy (MIBI; Fig. 20.18), ^{99m}Tc single-photon emission computed tomography (SPECT)/CT and, most recently, fluorine-18 (^{18}F)-fluorocholine PET-CT. Negative imaging does not exclude the diagnosis, however, and four-gland exploration may be needed. Genetic testing should be considered when primary hyperparathyroidism is diagnosed before the age of 40, as the likelihood of underlying MEN syndromes is greater in this context.

Management

The treatment of choice for primary hyperparathyroidism is surgery, with excision of a solitary parathyroid adenoma or hyperplastic glands. Patients with parathyroid bone disease run a significant risk of developing hypocalcaemia post-operatively, but the risk of this can be reduced by correcting vitamin D deficiency pre-operatively.

Surgery is usually indicated for individuals with clear-cut symptoms or documented complications (such as renal stones, renal impairment or osteoporosis), and (in asymptomatic patients) significant hypercalcaemia (corrected serum calcium > 2.85 mmol/L (> 11.4 mg/dL)). Patients who are treated conservatively without surgery should have calcium biochemistry and renal function checked annually and bone density monitored periodically. They should be encouraged to maintain a high oral fluid intake to avoid renal stones.

Occasionally, primary hyperparathyroidism presents with severe life-threatening hypercalcaemia. This is often due to dehydration and should be managed medically with intravenous fluids and bisphosphonates, as described on page 171. If this is not effective, then urgent parathyroidectomy should be considered.

Cinacalcet is a calcimimetic that enhances the sensitivity of the calcium-sensing receptor, and thus reduces PTH levels. It is licensed for tertiary hyperparathyroidism (p. 633) and as a treatment for patients with primary hyperparathyroidism who are unwilling to have surgery or are medically unfit. However, unlike parathyroid surgery, there is no evidence that cinacalcet reduces the risk of primary hyperparathyroidism–related end-organ damage.

Familial hypocalciuric hypercalcaemia

This autosomal dominant disorder is most commonly caused by an inactivating variant in one of the alleles of the *CASR* gene, which reduces the sensitivity of the parathyroid gland to ionised calcium concentrations. As a result, higher than normal calcium levels are required to suppress PTH secretion. The typical presentation is with mild hypercalcaemia with PTH concentrations that are 'inappropriately' at the upper end of the reference range or are slightly elevated. Calcium-sensing receptors in the renal tubules are also affected and this leads to increased renal tubular reabsorption of calcium and hypocalciuria (as measured in the vitamin D-replete individual by a fractional calcium excretion or 24-hour calcium excretion). The hypercalcaemia of FHH is asymptomatic and complications generally do not occur. The main risk of FHH is that of the patient being subjected to an unnecessary (and ineffective) parathyroidectomy if misdiagnosed as having primary hyperparathyroidism. Testing of family members for hypercalcaemia is helpful in confirming the diagnosis and it is also possible to perform genetic testing. No treatment is necessary.

Hypoparathyroidism

The most common cause of hypoparathyroidism is damage to the parathyroid glands (or their blood supply) during thyroid surgery. Rarely, hypoparathyroidism can occur as a result of infiltration of the glands with iron in haemochromatosis or copper in Wilson disease.

There are a number of rare congenital or inherited forms of hypoparathyroidism. One form is associated with autoimmune polyendocrine syndrome type 1 (p. 742) and another with DiGeorge syndrome. Autosomal dominant hypoparathyroidism is the mirror image of FHH (see above), in that an activating variant in the *CASR* gene reduces PTH levels, resulting in hypocalcaemia and hypercalciuria.

Pseudohypoparathyroidism

In this disorder, the individual is functionally hypoparathyroid but, instead of PTH deficiency, there is tissue resistance to the effects of PTH, such that PTH concentrations are markedly elevated. The PTH receptor itself is normal but the downstream signalling pathways are defective due to mutations that affect *GNAS1*, which encodes the Gsα protein, a molecule involved in signal transduction downstream of the PTH receptor and other G protein–coupled receptors. There are several subtypes but the most common (pseudohypoparathyroidism type 1a) is characterised by hypocalcaemia and hyperphosphataemia, in association with short stature, short fourth metacarpals and metatarsals, rounded face, obesity and subcutaneous calcification; these features are collectively referred to as Albright hereditary osteodystrophy (AHO). Type 1a pseudohypoparathyroidism occurs only when the *GNAS1* pathogenic variant is inherited on the maternal chromosome.

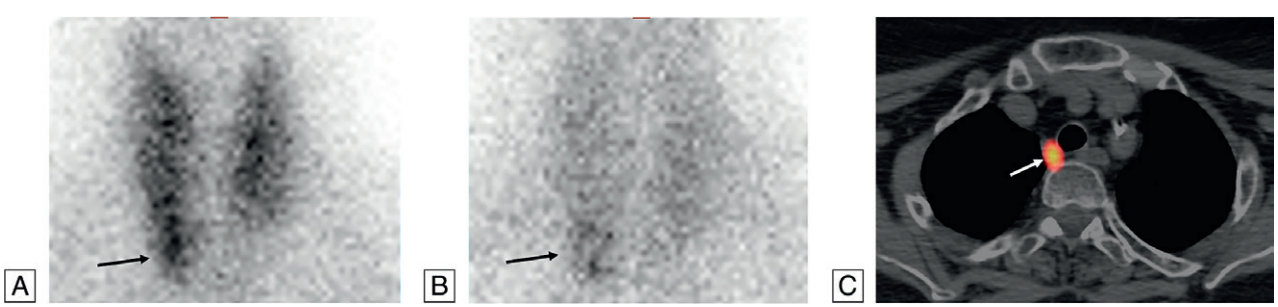

Fig. 20.18 A Early and B late planar ^{99m}Tc sestamibi scans demonstrating uptake of isotope within the thyroid gland and a right inferior parathyroid adenoma (arrow) on the early phase scan with retention of isotope within the parathyroid adenoma and washout of isotope from the thyroid gland on the late phase scan. C SPECT/CT allows precise anatomical location of the adenoma adjacent to the right posterior wall of the trachea (arrow) facilitating targeted surgical resection.

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The term pseudopseudohypoparathyroidism is used to describe patients who have clinical features of AHO but normal serum calcium and PTH concentrations; it occurs when the *GNAS1* pathogenic variant is inherited on the paternal chromosome. The inheritance of these disorders is an example of genetic imprinting (see Ch. 3). The difference in clinical features occurs as a result of the fact that renal cells exclusively express the maternal *GNAS1* allele, whereas both maternal and paternal alleles are expressed in other cell types.

Management of hypoparathyroidism

Persistent hypoparathyroidism and pseudohypoparathyroidism are treated with oral calcium salts and vitamin D analogues, either 1α-hydroxycholecalciferol (alfacalcidol) or 1,25-dihydroxycholecalciferol (calcitriol). This therapy needs careful monitoring because of the risks of iatrogenic hypercalcaemia, hypercalciuria and nephrocalcinosis. Recombinant PTH is available as a subcutaneous injection and has been used in hypoparathyroidism (but not in pseudohypoparathyroidism as it would not be effective). It is much more expensive than calcium and vitamin D analogues and remains a second-line therapy but has the advantage that it is less likely to cause hypercalciuria. There is no specific treatment for pseudohypoparathyroidism other than to try to maintain calcium levels within the reference range using active vitamin D metabolites.

The adrenal glands

The adrenals comprise several separate endocrine glands within a single anatomical structure. The adrenal medulla is an extension of the sympathetic nervous system that secretes catecholamines into capillaries rather than synapses. Most of the adrenal cortex is made up of cells that secrete cortisol and adrenal androgens, and form part of the hypothalamic–pituitary–adrenal (HPA) axis. The small outer glomerulosa of the cortex secretes aldosterone under the control of the renin–angiotensin system. These functions are important in the integrated control of cardiovascular, metabolic and immune responses to stress.

There is increasing evidence that subtle alterations in adrenal function contribute to the pathogenesis of common diseases such as hypertension, obesity and type 2 diabetes mellitus. However, classical syndromes of adrenal hormone deficiency and excess are relatively rare.

Functional anatomy and physiology

Adrenal anatomy and function are shown in Figure 20.19. Histologically, the cortex is divided into three zones, but these function as two units (zona glomerulosa and zonae fasciculata/reticularis) that produce

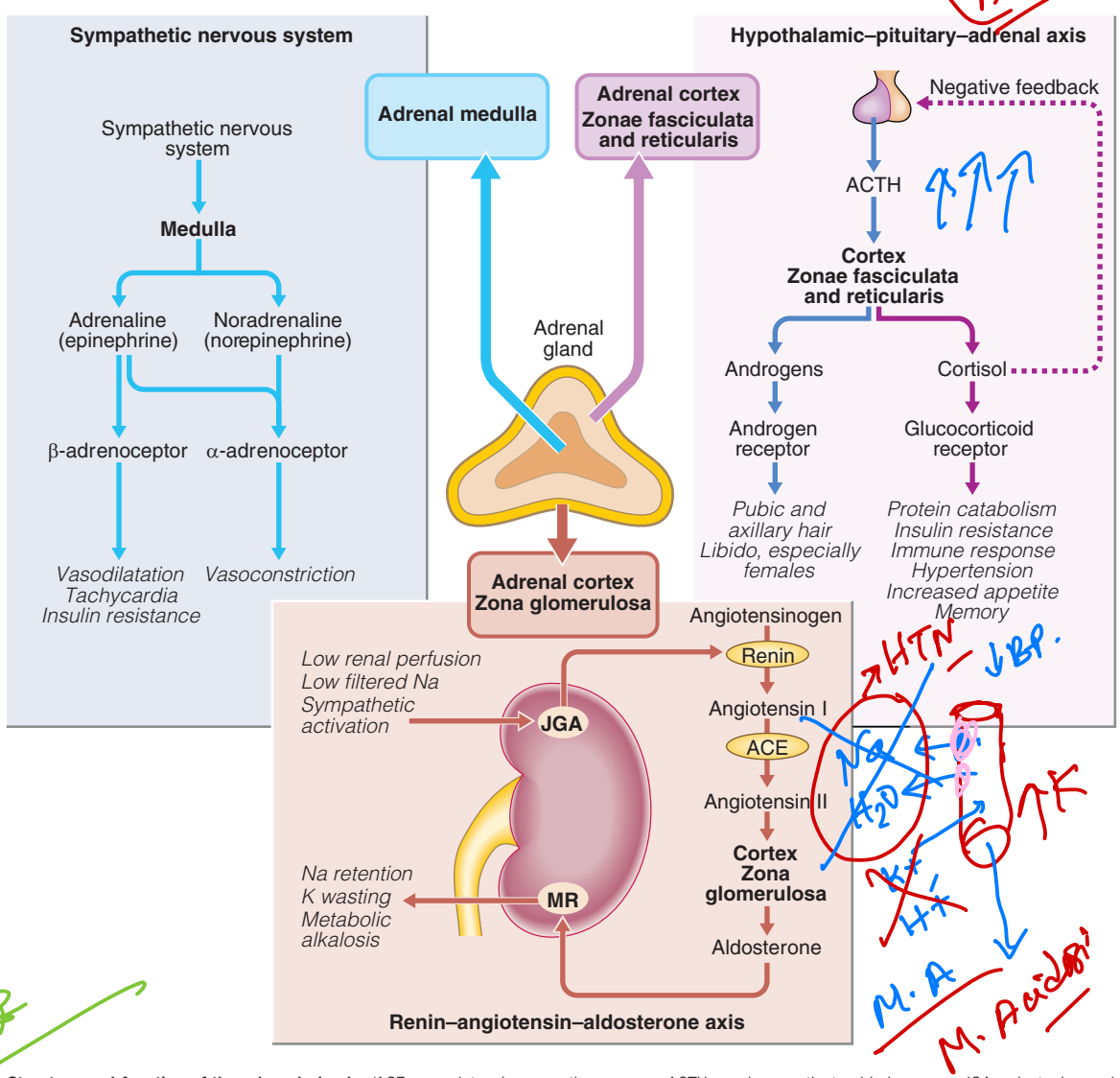

Fig. 20.19 Structure and function of the adrenal glands. (ACE = angiotensin-converting enzyme; ACTH = adrenocorticotrophic hormone; JGA = juxtaglomerular apparatus; MR = mineralocorticoid receptor)

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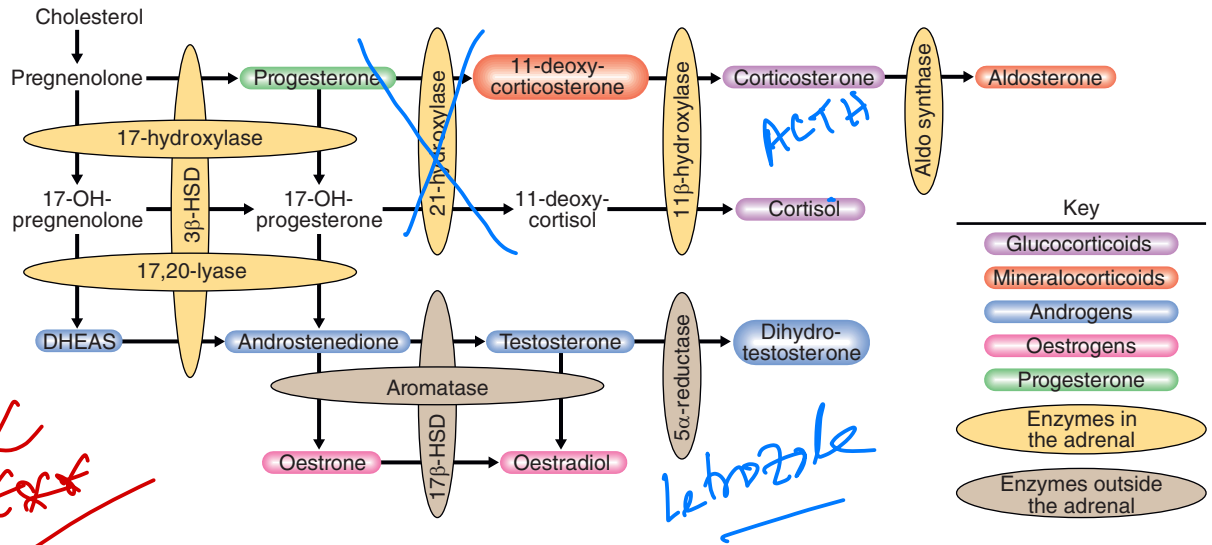

Fig. 20.20 The major pathways of synthesis of steroid hormones. (DHEAS = dehydroepiandrosterone sulphate; HSD = hydroxysteroid dehydrogenase)

i 20.36 Classification of diseases of the adrenal glands

	Primary	Secondary
Hormone excess	Non-ACTH-dependent Cushing syndrome Primary hyperaldosteronism Phaeochromocytoma	ACTH-dependent Cushing syndrome Secondary hyperaldosteronism
Hormone deficiency	Addison disease Congenital adrenal hyperplasia	Hypopituitarism Opioid analgesia
Hormone hypersensitivity	11β-hydroxysteroid dehydrogenase type 2 deficiency Liddle syndrome	
Hormone resistance	Pseudohypoaldosteronism Glucocorticoid resistance syndrome	
Non-functioning tumours	Adenoma Carcinoma (usually functioning) Metastatic tumours	

(ACTH = adrenocorticotrophic hormone)

corticosteroids in response to humoral stimuli. Pathways for the biosynthesis of corticosteroids are shown in Figure 20.20. Investigation of adrenal function is described under specific diseases below. The different types of adrenal disease are shown in Box 20.36.

Glucocorticoids

Cortisol is the major glucocorticoid in humans. Levels are highest in the morning on waking and lowest in the middle of the night. Cortisol rises dramatically during stress, including any illness. This elevation protects key metabolic functions (such as the maintenance of cerebral glucose supply during starvation) and inhibits potentially damaging inflammatory responses to infection and injury. The clinical importance of cortisol deficiency is, therefore, most obvious at times of stress.

More than 95% of circulating cortisol is bound to protein, principally cortisol-binding globulin, which is increased by oestrogens. It is the free fraction that is biologically active. Cortisol regulates cell function by binding to glucocorticoid receptors, which regulate the transcription of many genes. Cortisol can also activate mineralocorticoid receptors, but it does not normally do so because most cells containing mineralocorticoid receptors also express an enzyme called 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which inactivates cortisol by converting it to cortisone. Inhibitors of 11β-HSD2 (such as some liquorice) or pathogenic variants in the gene that encodes 11β-HSD2 cause cortisol to act as a mineralocorticoid, resulting in sodium retention and hypertension (see Box 20.45).

Mineralocorticoids

Aldosterone is the most important mineralocorticoid. It binds to mineralocorticoid receptors in the kidney and causes sodium retention and increased excretion of potassium and hydrogen ions (see Fig. 19.2). The principal stimulus to aldosterone secretion is angiotensin II, a peptide produced by activation of the renin–angiotensin system (see Fig. 20.19). Renin activity in the juxtaglomerular apparatus of the kidney is stimulated by low perfusion pressure in the afferent arteriole, low sodium filtration leading to low sodium concentrations at the macula densa, or increased sympathetic nerve activity. As a result, renin activity is increased in hypovolaemia and renal artery stenosis, and is approximately doubled when standing up from a recumbent position.

Catecholamines

In humans, only a small proportion of circulating noradrenaline (norepinephrine) is derived from the adrenal medulla; much more is released from sympathetic nerve endings. Conversion of noradrenaline to adrenaline (epinephrine) is catalysed by phenylethanolamine N-methyltransferase (PNMT), which is induced by glucocorticoids. Blood flow in the adrenal is centripetal, so that the medulla is bathed in high concentrations of cortisol and is the major source of circulating adrenaline. However, after surgical removal of the adrenal medullae, there appear to be no clinical consequences attributable to deficiency of circulating catecholamines.

Adrenal androgens

Adrenal androgens are secreted in response to ACTH and are the most abundant steroids in the blood stream. They are probably important in the initiation of puberty (adrenarche). The adrenals are also the major source of androgens in adult females and may be important in female libido.

Presenting problems in adrenal disease

Cushing syndrome

Cushing syndrome is caused by excessive activation of glucocorticoid receptors. It is most commonly iatrogenic, due to prolonged administration of synthetic glucocorticoids such as prednisolone. Endogenous

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Cushing syndrome is uncommon but is caused by chronic over-production of cortisol by the adrenal glands, either as the result of an adrenal tumour or because of excessive production of ACTH by a pituitary tumour or ectopic ACTH production by other tumours.

Aetiology

The causes are shown in Box 20.37. Amongst endogenous causes, pituitary-dependent cortisol excess (by convention, called Cushing disease) accounts for approximately 80% of cases. Both Cushing disease and cortisol-secreting adrenal tumours are four times more common in women than men. In contrast, ectopic ACTH syndrome (often due to a small-cell carcinoma of the bronchus) is more common in men.

20.37 Classification of endogenous Cushing syndrome

ACTH-dependent – 80%

- Pituitary adenoma secreting ACTH (Cushing disease) – 70%
- Ectopic ACTH syndrome (bronchial carcinoid, small-cell lung carcinoma, other neuroendocrine tumour) – 10%

Non-ACTH-dependent – 20%

- Adrenal adenoma – 15%
- Adrenal carcinoma – 5%
- ACTH-independent macronodular hyperplasia; primary pigmented nodular adrenal disease; McCune–Albright syndrome (together < 1%)

Hypercortisolism due to other causes (also referred to as pseudo-Cushing syndrome)

- Alcohol excess (biochemical and clinical features)
- Major depressive illness (biochemical features only, some clinical overlap)
- Primary obesity (mild biochemical features, some clinical overlap)

(ACTH = adrenocorticotrophic hormone)

Clinical assessment

The diverse manifestations of glucocorticoid excess are shown in Figure 20.21. Many of these are not specific to Cushing syndrome and, because spontaneous Cushing syndrome is rare, the positive predictive value of any single clinical feature alone is low. Moreover, some common disorders can be confused with Cushing syndrome because they are associated with alterations in cortisol secretion, e.g. obesity and depression (see Box 20.37). Features that favour Cushing syndrome in an obese patient are those of protein-wasting, including bruising, proximal myopathy and thin skin. Any clinical suspicion of cortisol excess is best resolved by further investigation.

It is vital to exclude iatrogenic causes in all patients with Cushing syndrome since even inhaled or topical glucocorticoids can induce the syndrome in susceptible individuals. A careful drug history must therefore be taken before embarking on complex investigations. An 0800–0900 hrs serum cortisol of < 100 nmol/L (3.6 μg/dL) in a patient with a normal sleep–wake pattern and Cushingoid appearance is consistent with exogenous synthetic glucocorticoid use (common); however, morning cortisol measurement cannot be used as a diagnostic test to confirm the presence of endogenous glucocorticoid excess.

Some clinical features are more common in ectopic ACTH syndrome. While ACTH-secreting pituitary tumours retain some negative feedback sensitivity to cortisol, this is absent in tumours that produce ectopic ACTH, typically resulting in higher levels of both ACTH and cortisol than are observed in pituitary-driven disease. The high ACTH levels are associated with marked pigmentation because of binding to melanocortin 1 receptors on melanocytes in the skin. The high cortisol

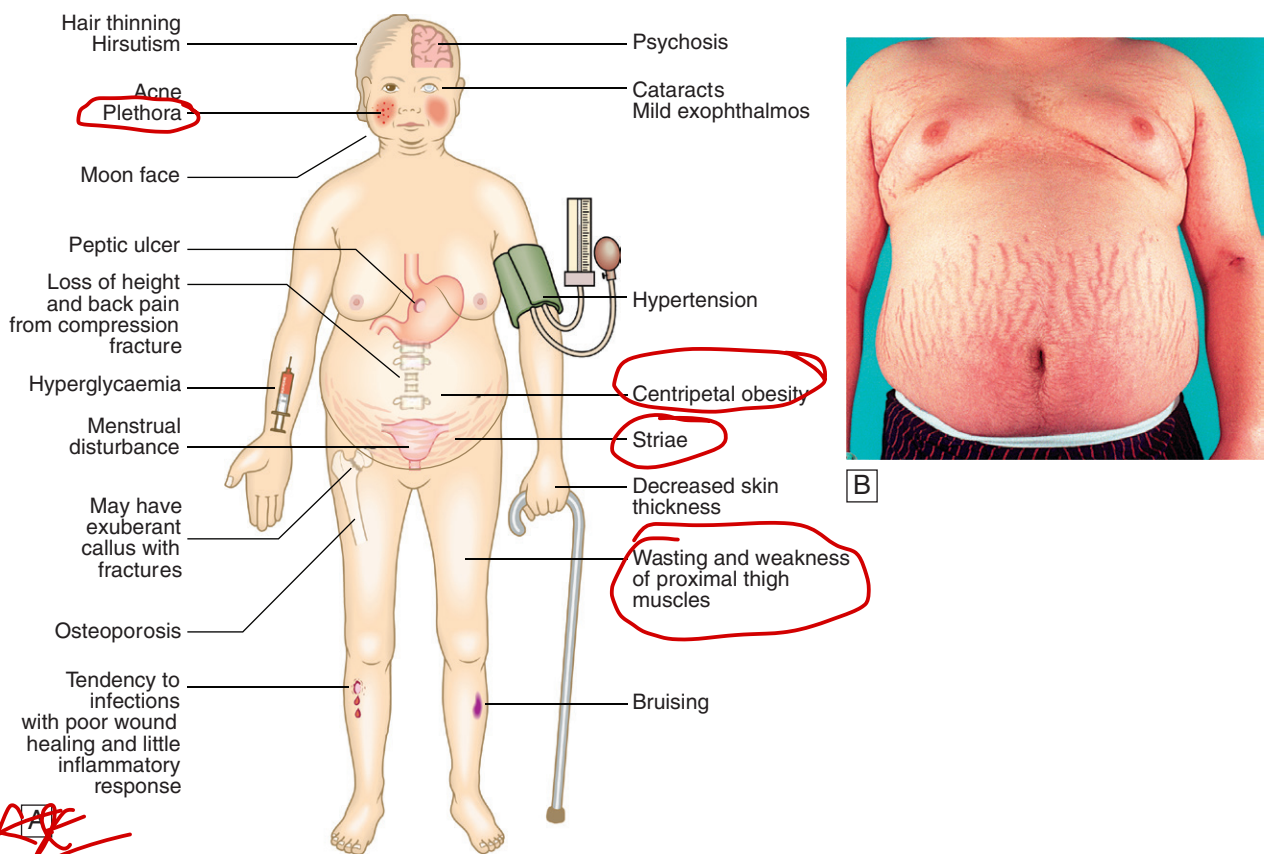

Fig. 20.21 Cushing syndrome. A Clinical features common to all causes. B A patient with Cushing syndrome. *(B) From Chew SL, Leslie D. Clinical endocrinology and diabetes: an illustrated colour text. Churchill Livingstone; 2006.*

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levels also overcome the capacity of 11β-HSD2 to inactivate cortisol in the kidney, causing hypokalaemic alkalosis, which aggravates myopathy and hyperglycaemia (by inhibiting insulin secretion). When the tumour that is secreting ACTH is malignant, the onset is usually rapid and may be associated with cachexia. For these reasons, the classical features of Cushing syndrome are less common in ectopic ACTH syndrome; if present, they suggest that a less aggressive tumour, such as a bronchial carcinoid, is responsible.

In Cushing disease, the pituitary tumour is usually a microadenoma (≤10 mm in diameter); hence other features of a pituitary macroadenoma (visual failure or disconnection hyperprolactinaemia, p. 737) are rare, but there may be secondary hypogonadism due to the inhibitory effects of excess glucocorticoids on gonadotrophin secretion. If a diagnosis of Cushing disease is suspected, early discussion/referral to a specialist is recommended.

Investigations

The large number of tests available for Cushing syndrome reflects the fact that each one has limited specificity and sensitivity in isolation. Accordingly, several tests are usually combined to establish the diagnosis. Testing for Cushing syndrome should be avoided under conditions of stress, such as an acute illness, because this activates the HPA axis, causing potentially spurious results. The diagnosis of Cushing syndrome is a two-step process (Fig. 20.22):

1. to establish whether the patient has Cushing syndrome, and
2. to define its cause.

Some additional tests are useful in all cases of Cushing syndrome, including plasma electrolytes, glucose, glycosylated haemoglobin and bone mineral density measurement.

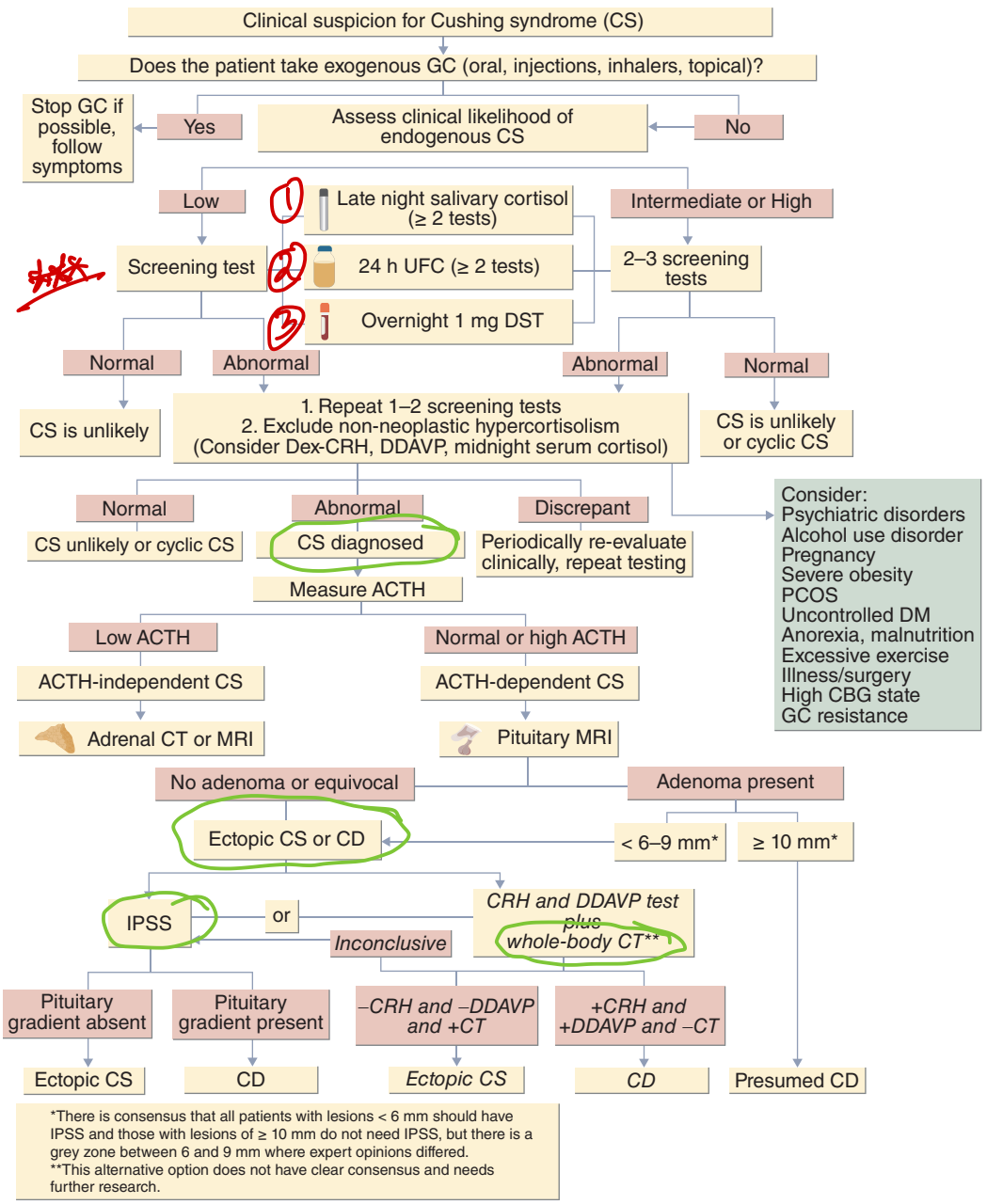

Fig. 20.22 Sequence of investigations in suspected Cushing syndrome. (ACTH = adrenocorticotrophic hormone; CBG = corticosteroid-binding globulin; CD = Cushing disease; CRH = corticotrophin-releasing hormone; CS = Cushing syndrome; CT = computed tomography scan; DDAVP = 1-deamino-8-D-arginine vasopressin; Dex = dexamethasone; DM = diabetes mellitus; DST = dexamethasone suppression test; GC = glucocorticoid; IPSS = inferior petrosal sinus sampling; MRI = magnetic resonance imaging; PCOS, polycystic ovary syndrome; UFC = urinary free cortisol)

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Establishing the presence of Cushing syndrome

In patients where there is appropriate clinical suspicion, Cushing syndrome is confirmed by using two of three main tests:

1. Failure to suppress serum cortisol with low doses of oral dexamethasone
2. Loss of the normal circadian rhythm of cortisol, with inappropriately elevated late-night serum or salivary cortisol
3. Increased 24-hour urine free cortisol (lower sensitivity than the above tests) (see Fig. 20.22).

Dexamethasone is used for suppression testing because it does not cross-react in immunoassays for cortisol. An overnight dexamethasone suppression test (ONDST) involves administration of 1 mg dexamethasone at 2300 hrs and measurement of serum cortisol at 0900 hrs the following day; a normal response is a serum cortisol of < 50 nmol/L (1.8 µg/dL). It is important for any oestrogens to be stopped for 6 weeks prior to investigation to allow corticosteroid-binding globulin (CBG) levels to return to normal and to avoid false-positive responses, as most cortisol assays measure total cortisol, including that bound to CBG. Cyclicity of cortisol secretion is a feature of all types of Cushing syndrome and, if very variable, can confuse diagnosis. Use of multiple salivary cortisol samples over weeks or months can be helpful in diagnosis, but an elevated salivary cortisol alone should not be taken as proof of diagnosis. In iatrogenic Cushing syndrome, cortisol levels are low unless the patient is taking a glucocorticoid (such as prednisolone) that cross-reacts in immunoassays with cortisol.

Determining the underlying cause

Once the presence of Cushing syndrome is confirmed, measurement of plasma ACTH is the key to establishing the differential diagnosis; it is best measured in the morning around 0900 hrs. Low ACTH is indicative of a primary adrenal source. CT or MRI detects most adrenal tumours; adrenal carcinomas are usually large (> 5 cm) and have other features of malignancy. Where ACTH is normal or high, a pituitary MRI scan should be performed to determine whether a pituitary adenoma can be identified. Where pituitary MRI identifies a macroadenoma (≥ 10 mm), this is typically regarded as sufficient to confirm a pituitary source of ACTH excess (Cushing disease). More commonly, a smaller adenoma or no adenoma is identified and, in this eventuality, further tests are recommended to distinguish between a pituitary source or ectopic ACTH secretion (this is because small, non-functioning pituitary 'incidentalomas' are common and so a pituitary microadenoma cannot be presumed to be the source of ACTH). If available, inferior petrosal sinus sampling (IPSS) with measurement of plasma ACTH and a comparison of the results to peripheral levels is the best means of confirming Cushing disease (increased central:peripheral gradient). An alternative approach, where IPSS is unavailable, is corticotrophin-releasing hormone (CRH) and 1-deamino-8-D-arginine vasopressin (DDAVP) testing, plus whole-body CT (although global supply issues are likely to compromise CRH availability for the foreseeable future) (see Fig. 20.22).

Management

Untreated severe Cushing syndrome has a 50% 5-year mortality. Most patients are treated surgically, but medical therapy may be given in severe cases for a few weeks prior to operation to optimise perioperative health, or where there is recurrent or incurable disease. Drugs that inhibit glucocorticoid biosynthesis (metyrapone, ketoconazole and osilodrostat) form the mainstay of management. The dose of these agents is best titrated against serum cortisol levels or 24-hour urine free cortisol.

Cushing disease

Trans-sphenoidal surgery carried out by an experienced surgeon with selective removal of the adenoma is the treatment of choice, with approximately 70% of patients going into immediate remission. Around 20% of patients suffer a recurrence, often years later, emphasising the need for life-long follow-up.

Laparoscopic bilateral adrenalectomy performed by an expert surgeon effectively cures any type of ACTH-dependent Cushing syndrome, but in patients with Cushing disease (pituitary) this can result in Nelson syndrome – an invasive pituitary macroadenoma (which causes local mass effects) and very high ACTH levels (which cause pigmentation). The risk of Nelson syndrome is reported to be reduced by pituitary irradiation in some series, but not all.

The somatostatin analogue pasireotide is also licensed for the treatment of Cushing disease and works by suppressing ACTH secretion by the tumour.

Adrenal tumours

Laparoscopic adrenal surgery is the treatment of choice for adrenal adenomas. Surgery offers the only prospect of cure for adrenocortical carcinomas but, in general, prognosis is poor with high rates of recurrence, even in patients with localised disease at presentation. Radiotherapy to the tumour bed reduces the risk of local recurrence; systemic therapy consists of the adrenolytic drug mitotane and chemotherapy, but responses are often poor.

Ectopic ACTH syndrome

Localised tumours, such as bronchial carcinoids, should be removed surgically. In patients with incurable malignancy, it is important to reduce the severity of the Cushing syndrome using medical therapy (see above) or, if appropriate, bilateral adrenalectomy.

Therapeutic use of glucocorticoids

The remarkable anti-inflammatory properties of glucocorticoids have led to their use in a wide variety of clinical conditions but the hazards are significant. Equivalent doses of commonly used glucocorticoids are listed in Box 20.38. Topical preparations (dermal, rectal and inhaled) can also be absorbed into the systemic circulation, and although this rarely occurs to a sufficient degree to produce clinical features of Cushing syndrome, it can result in significant suppression of endogenous ACTH and cortisol secretion. Severe Cushing syndrome can result if there is concomitant administration of inhaled glucocorticoids and strong inhibitors of the liver enzyme CYP450 3A4, such as the antiretroviral drug ritonavir.

Adverse effects of glucocorticoids

The clinical features of glucocorticoid excess are illustrated in Figure 20.21. Adverse effects are related to dose, duration of therapy, and pre-existing conditions that might be worsened by glucocorticoid therapy, such as diabetes mellitus or osteoporosis. Osteoporosis is a particularly important problem because, for a given bone mineral density, the fracture risk is greater in glucocorticoid-treated patients than in post-menopausal osteoporosis. Therefore, when systemic glucocorticoids are prescribed and the anticipated duration of therapy is more than 3 months, bone-protective therapy should be considered. Rapid changes in glucocorticoid levels can also lead to marked mood disturbances, including depression, mania and insomnia. Glucocorticoid use also increases the white blood cell count (predominantly neutrophils), which must be taken into account when assessing patients with possible infection.

The anti-inflammatory effect of glucocorticoids may mask signs of disease. For example, perforation of a viscus may be masked and the patient may show no febrile response to an infection. Although there is debate about whether or not glucocorticoids increase the risk of peptic ulcer when used alone, they act synergistically with NSAIDs, including aspirin, to increase the risk of serious gastrointestinal adverse effects.

20.38 Approximate equivalent doses of glucocorticoids

- Hydrocortisone: 20 mg
- Cortisone acetate: 25 mg
- Prednisolone: 5 mg
- Dexamethasone: 0.5 mg

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Latent tuberculosis may be reactivated and patients on glucocorticoids are at risk of severe varicella zoster virus infection, so should avoid contact with chickenpox or shingles if they are non-immune.

Management of glucocorticoid withdrawal

All glucocorticoid therapy, even if inhaled or applied topically, can suppress the HPA axis. In practice, this is likely to result in a crisis due to adrenal insufficiency on withdrawal of treatment only if glucocorticoids have been administered orally or systemically for longer than 4 weeks, if repeated courses have been prescribed within the previous year, or if the dose is higher than the equivalent of 5 mg prednisolone per day. In these circumstances, the drug, when it is no longer required for the underlying condition, must be withdrawn slowly at a rate dictated by the duration of treatment. If glucocorticoid therapy has been prolonged, then it may take many months for the HPA axis to recover. All patients must be advised to avoid sudden drug withdrawal. They should be issued with a steroid emergency card and/or wear an engraved bracelet (Box 20.39).

Recovery of the HPA axis is aided if there is no exogenous glucocorticoid present during the nocturnal surge in ACTH secretion. This can be achieved by giving glucocorticoid in the morning. Giving ACTH to stimulate adrenal recovery is of no value, as the pituitary remains suppressed.

Patients who have received supraphysiological glucocorticoids (5 mg of prednisolone or equivalent or more) for longer than four weeks, in whom the dose has dropped below a physiological equivalent, should be monitored for signs and symptoms of adrenal insufficiency and provided advice to cover 'sick days' with 10 mg prednisolone or equivalent as per the steroid emergency card (see Box 20.39). Adrenal function can be assessed biochemically (once the dose of glucocorticoid is below 5 mg prednisolone or equivalent) by measuring serum cortisol at 0800–0900 hrs prior to taking glucocorticoid medication. A morning cortisol over 300 nmol/L is reassuring in this context as >99% of these patients would pass a stimulation test. In patients with a morning cortisol <300 nmol/L, ACTH stimulation testing may help to determine adequacy of adrenal function. Glucocorticoid treatment can stop if adequate adrenal function has been demonstrated; however, if adrenal function is inadequate then encouraging recovery with a period of sub-physiological replacement (<4 mg prednisolone or equivalent with sick day advice) may be necessary with repeat testing after 3–6 months. The thresholds cited above are for guidance only and may vary depending on the cortisol assay used. Even when glucocorticoids have been successfully withdrawn, short-term replacement therapy is often advised during significant intercurrent illness occurring in subsequent months, as the HPA axis may not be able to respond fully to severe stress.

20.39 Advice to patients on glucocorticoid replacement therapy

Intercurrent stress
- Febrile illness: double dose of hydrocortisone

Surgery
- Minor operation: hydrocortisone 100 mg IV with pre-medication
- Major operation: hydrocortisone 100 mg IV 4 times daily for 24 hrs, then 50 mg IV 4 times daily until ready to take tablets

Vomiting
- Patients must have parenteral hydrocortisone if unable to take it by mouth

Steroid card
- Patient should carry this at all times; it should give information regarding diagnosis, steroid, dose and doctor

Bracelet and emergency pack
- Patients should be encouraged to buy a bracelet and have it engraved with the diagnosis, current treatment and a reference number for a central database
- Patients should be given a hydrocortisone emergency pack and trained in the self-administration of hydrocortisone 100 mg IM; they should be advised to take the pack on holidays/trips abroad

(IM = intramuscular; IV = intravenous)

Adrenal insufficiency

Adrenal insufficiency (AI) results from inadequate secretion of cortisol and/or aldosterone. It is potentially fatal and notoriously variable in its presentation. A high index of suspicion is therefore required in patients with unexplained fatigue, hyponatraemia or hypotension. Causes are shown in Box 20.40. The most common is ACTH deficiency (secondary AI), usually because of inappropriate withdrawal of chronic glucocorticoid therapy or a large pituitary tumour. Addison disease is often used as a collective term for primary AI, but strictly speaking refers to destructive processes involving the adrenal cortex, such as autoimmune disease and tuberculosis.

Clinical assessment

The clinical features of adrenal insufficiency are shown in Box 20.41. In primary AI, either glucocorticoid or mineralocorticoid deficiency may come first, but eventually all patients fail to secrete both classes of corticosteroid (and adrenal androgens).

Patients may present with chronic features and/or in acute circulatory shock. With a chronic presentation, initial symptoms are often misdiagnosed as chronic fatigue syndrome or depression. In primary AI, weight loss is a uniform presenting feature. AI should also be considered in patients with hyponatraemia, even in the absence of symptoms.

Features of an acute adrenal crisis include circulatory shock with severe hypotension, hyponatraemia, hyperkalaemia and, in some instances, hypoglycaemia and hypercalcaemia. Muscle cramps, nausea, vomiting, diarrhoea and unexplained fever may be present. The crisis is often precipitated by intercurrent disease, surgery or infection.

Vitiligo occurs in 10%–20% of patients with autoimmune Addison disease.

Investigations

Treatment should not be delayed in patients with suspected acute adrenal crisis. A random blood sample should be taken for measurement of serum cortisol and, if possible, plasma ACTH; if the patient's clinical condition permits, it may be appropriate to spend 30 minutes performing an ACTH stimulation test (Box 20.42) before administering

20.40 Causes of adrenal insufficiency

Secondary (↓ACTH)
- Withdrawal of suppressive glucocorticoid therapy
- Hypothalamic or pituitary disease

Primary (↑ACTH)

Common destructive causes
- Autoimmune:
  - Sporadic
  - Polyendocrine syndromes (APS types 1 and 2)
- Tuberculosis
- HIV
- CMV
- Metastatic carcinoma
- Bilateral adrenalectomy

Rare destructive causes
- Lymphoma
- Intra-adrenal haemorrhage (Waterhouse–Friderichsen syndrome following meningococcal sepsis)
- Amyloidosis

Haemochromatosis

Corticosteroid biosynthetic enzyme defects
- Congenital adrenal hyperplasias
- Drugs: metyrapone, ketoconazole, etomidate

(ACTH = adrenocorticotrophic hormone; APS = autoendocrine polyendocrine syndromes; CMV = cytomegalovirus; HIV = human immunodeficiency virus)

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20.41 Clinical and biochemical features of adrenal insufficiency

	Glucocorticoid insufficiency	Mineralocorticoid insufficiency	ACTH excess	Adrenal androgen insufficiency
Withdrawal of exogenous glucocorticoid	+	–	–	+
Hypopituitarism	+	–	–	+
Addison disease	+	+	+	+
Congenital adrenal hyperplasia (21-hydroxylase deficiency)	+	+	+	–
Clinical features	Weight loss, anorexia Malaise, weakness Nausea, vomiting Diarrhoea or constipation Postural hypotension Shock Hypoglycaemia Hyponatraemia (dilutional) Hypercalcaemia	Hypotension Shock Hyponatraemia (depletional) Hyperkalaemia	Pigmentation of: Sun-exposed areas Pressure areas (e.g. elbows, knees) Palmar creases, knuckles Mucous membranes Conjunctivae Recent scars	Decreased body hair and loss of libido, especially in females

(ACTH = adrenocorticotrophic hormone)

20.42 How and when to do an ACTH stimulation test*

Use

- Diagnosis of primary or secondary adrenal insufficiency
- Assessment of HPA axis in patients taking suppressive glucocorticoid therapy
- Relies on ACTH-dependent adrenal atrophy in secondary adrenal insufficiency, so may not detect acute ACTH deficiency (e.g. in pituitary apoplexy)

Dose

- 250 μg $ACTH_{1–24}$ (Synacthen) by IM injection at any time of day

Blood samples

- 0 and 30 mins for plasma cortisol
- 0 mins also for ACTH (on ice) if Addison disease is being considered (patient not known to have pituitary disease or to be taking exogenous glucocorticoids)

Results

- Normal subjects: plasma cortisol > 430 nmol/L (approximately 15.6 μg/dL) either at baseline or at 30 mins
- Incremental change in cortisol is not a criterion

*May also be referred to as 'short Synacthen', cosyntropin, corticotropin or tetracosactide test
(ACTH = adrenocorticotrophic hormone; HPA = hypothalamic–pituitary–adrenal; IM = intramuscular)

hydrocortisone, but delays must be avoided if there is circulatory compromise. Investigations should be performed before treatment is given in patients who present with features suggestive of chronic adrenal insufficiency.

Assessment of glucocorticoids

Random serum cortisol is usually low in patients with AI but it may be within the reference range, yet inappropriately low, for a seriously ill patient. Random measurement of serum cortisol cannot therefore be used to confirm or refute the diagnosis, unless the value is above 430 nmol/L (> 15.6 μg/dL), which effectively excludes AI. However, random cortisol > 300 nmol/L is almost never associated with AI and may be sufficiently reassuring where the clinical index of suspicion (pre-test probability) is low. It is important to note that thresholds cited here are indicative and will vary between different cortisol assays. More useful is the ACTH stimulation test described in Box 20.42. Cortisol levels fail to increase in response to exogenous ACTH in patients with primary or secondary AI. These can be distinguished by measurement of ACTH (which is low in secondary AI and high in primary AI).

Assessment of mineralocorticoids

Mineralocorticoid secretion in patients with suspected primary AI cannot be adequately assessed by electrolyte measurements since hyponatraemia occurs in both aldosterone and cortisol deficiency (see Box 20.41). Hyperkalaemia is common, but not universal, in aldosterone deficiency. Plasma renin and aldosterone should be measured in the supine position. In mineralocorticoid deficiency, plasma renin activity is high, with plasma aldosterone being either low or in the lower part of the reference range.

Assessment of adrenal androgens

This is not necessary in men because testosterone from the testes is the principal androgen. In women, dehydroepiandrosterone sulphate (DHEAS) and androstenedione may be measured in a random specimen of blood, though levels are highest in the morning.

Other tests to establish the cause

Patients with unexplained secondary AI should be investigated as described in Box 20.51. In patients with elevated ACTH, further tests are required to establish the cause of primary AI. Adrenal autoantibodies to 21-hydroxylase are frequently positive in autoimmune adrenal failure. If antibody tests are negative, imaging of the adrenal glands with CT or MRI is indicated. Tuberculosis causes adrenal calcification, visible on plain X-ray or ultrasound scan. A human immunodeficiency virus (HIV) test should be performed if relevant risk factors are present. Adrenal metastases are a rare cause of primary AI. Patients with evidence of autoimmune adrenal failure should be screened for other organ-specific autoimmune diseases, such as thyroid disease, pernicious anaemia and coeliac disease.

Management

Patients with AI always need glucocorticoid replacement therapy and usually, but not always, mineralocorticoid therapy. There is some evidence that adrenal androgen replacement may also be beneficial in some women. Other treatments depend on the underlying cause. The emergency management of adrenal crisis is described in Box 20.43.

Glucocorticoid replacement

Adrenal replacement therapy consists of oral hydrocortisone (cortisol) 15–20 mg daily in divided doses, typically 10 mg on waking and 5 mg at

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20.43 Management of adrenal crisis

Correct volume depletion

- IV saline as required to normalise blood pressure and pulse
- In severe hyponatraemia (< 125 mmol/L) avoid increases of plasma Na > 10 mmol/L/day to prevent pontine demyelination
- Fludrocortisone is not required during the acute phase of treatment

Replace glucocorticoids

- IV hydrocortisone succinate 100 mg stat, and 50 mg 4 times daily for first 12–24 hrs
- Continue parenteral hydrocortisone (50 mg IM 4 times daily) until patient is well enough for reliable oral therapy

Correct other metabolic abnormalities

- Acute hypoglycaemia: IV 10% glucose
- Hyperkalaemia: should respond to volume replacement but occasionally requires specific therapy (see Box 19.17)

Identify and treat underlying cause

- Consider acute precipitant, such as infection
- Consider adrenal or pituitary pathology (see Box 20.40)

(IM = intramuscular; IV = intravenous)

20.44 Glucocorticoids in old age

- **Adrenal insufficiency**: often insidious and may present with tiredness, drowsiness, delirium, falls, immobility and orthostatic hypotension.
- **Glucocorticoid therapy**: especially hazardous in older people, who are already relatively immunocompromised and susceptible to osteoporosis, diabetes, hypertension and other complications.
- **'Physiological' glucocorticoid replacement therapy**: increased risk of adrenal crisis because adherence may be poor and there is a greater incidence of intercurrent illness. Patient and carer education, with regular reinforcement of the principles described in Box 20.39, is crucial.

around 1500 hrs. These are physiological replacement doses that should not cause Cushingoid side-effects. The dose may need to be adjusted for the individual patient but this is subjective. Excess weight gain usually indicates over-replacement, while persistent lethargy or hyperpigmentation may be due to an inadequate dose or lack of absorption. Measurement of serum cortisol levels is not usually helpful. Advice to patients dependent on glucocorticoid replacement is given in Box 20.39 and considerations in respect of glucocorticoids in old age are given in Box 20.44.

Mineralocorticoid replacement

Fludrocortisone (9α-fluoro-hydrocortisone) is administered at the usual dose of 0.05–0.15 mg daily, and adequacy of replacement may be assessed by measurement of blood pressure, plasma electrolytes and plasma renin. It is indicated for virtually every patient with primary AI, but is not needed in secondary AI.

Androgen replacement

Androgen replacement with DHEAS (25–50 mg/day) is occasionally given to women with primary AI who have symptoms of reduced libido and fatigue, but the evidence in support of this is not robust and treatment may be associated with side-effects such as acne and hirsutism.

Incidental adrenal mass

Enlarged or hyperplastic adrenal glands are commonly found on CT or MRI scans of the abdomen that have been performed for other indications. Such lesions are known as adrenal 'incidentalomas'. The prevalence increases with age and they are present in up to 10% of adults aged 70 years and older.

Sixty per cent of adrenal incidentalomas are non-functioning adrenal adenomas. The remainder includes functional tumours of the adrenal cortex (secreting cortisol, aldosterone or androgens), phaeochromocytomas, primary and secondary carcinomas, hamartomas and other rare disorders, including granulomatous infiltrations. Bilateral masses are frequently identified and may be simple adrenal adenomas, but the diagnostic possibilities also include phaeochromocytomas, tuberculosis, primary adrenal lymphoma, metastatic disease and bilateral nodular hyperplasia.

Clinical assessment and investigations

There are two key questions to be resolved: is the lesion secreting hormones, and is it benign or malignant? These are best assessed by a dedicated adrenal multidisciplinary team (MDT).

Patients with an adrenal incidentaloma are usually asymptomatic. However, clinical signs and symptoms of excess glucocorticoids, mineralocorticoids, catecholamines and, in women, androgens should be sought, as discussed elsewhere in this chapter. Investigations should include a dexamethasone suppression test, urine or plasma metanephrines and, in virilised women, measurement of serum testosterone, DHEAS and androstenedione. Patients with hypertension should be investigated for mineralocorticoid excess, as described below.

CT and MRI are equally effective in assessing the malignant potential of an adrenal mass, using the following parameters:

- *Size*. The larger the lesion, the greater the malignant potential. Around 90% of adrenocortical carcinomas are over 4 cm in diameter, but specificity is poor since only approximately 25% of such lesions are malignant.
- *Configuration*. Homogeneous and smooth lesions are more likely to be benign. The presence of metastatic lesions elsewhere increases the risk of malignancy, but as many as two-thirds of adrenal incidentalomas in patients with cancer are benign.
- *Presence of lipid*. Adenomas are usually lipid-rich, resulting in an attenuation of ≤ 10 Hounsfield units (HU) on an unenhanced CT, and in signal dropout on chemical shift MRI.
- *Enhancement*. Benign lesions demonstrate rapid washout of contrast, whereas malignant lesions tend to retain contrast.

Histology in a sample obtained by CT-guided biopsy is rarely indicated, and is not useful in distinguishing an adrenal adenoma from an adrenocortical carcinoma. Biopsy is occasionally helpful in confirming adrenal metastases from other cancers, but should be avoided if either phaeochromocytoma or primary adrenal cancer is suspected in order to avoid precipitation of a hypertensive crisis or seeding of tumour cells, respectively. An endocrine opinion must be sought before any biopsy.

Management

Homogeneous lesions with attenuation ≤ 10 HU do not require intervention or follow-up, irrespective of size. Functional lesions and tumours of ≥ 4 cm that are inhomogeneous or have attenuation ≥ 20 HU should be considered for surgery. Intermediate lesions should be considered for radiological follow-up. Optimal management of patients with low-grade cortisol secretion (termed mild autonomous cortisol secretion), as demonstrated by the dexamethasone suppression test, remains to be established.

Primary hyperaldosteronism

Estimates of the prevalence of primary hyperaldosteronism vary according to the screening tests employed, but it may occur in as many as 10% of people with hypertension. Indications to test for mineralocorticoid excess in hypertensive patients include hypokalaemia (including hypokalaemia induced by thiazide diuretics), poor control of blood pressure with conventional therapy, a family history of early-onset hypertension, or presentation at a young age.

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20.45 Causes of mineralocorticoid excess

With renin high and aldosterone high (secondary hyperaldosteronism)

- Inadequate renal perfusion (diuretic therapy, cardiac failure, liver failure, nephrotic syndrome, renal artery stenosis)
- Renin-secreting renal tumour (very rare)

With renin low and aldosterone high (primary hyperaldosteronism)

- Adrenal adenoma secreting aldosterone (Conn syndrome)
- Idiopathic bilateral adrenal hyperplasia
- Glucocorticoid-suppressible hyperaldosteronism (rare)

With renin low and aldosterone low (non-aldosterone-dependent activation of mineralocorticoid pathway)

- Ectopic ACTH syndrome
- Liquorice misuse (inhibition of 11β-HSD2)
- Liddle syndrome
- 11-deoxycorticosterone-secreting adrenal tumour
- Rare forms of congenital adrenal hyperplasia and 11β-HSD2 deficiency

(11β-HSD2 = 11β-hydroxysteroid dehydrogenase type 2; ACTH = adrenocorticotrophic hormone)

Causes of excessive activation of mineralocorticoid receptors are shown in Box 20.45. It is important to differentiate primary hyperaldosteronism, caused by an intrinsic abnormality of the adrenal glands resulting in aldosterone excess, from secondary hyperaldosteronism, which is usually a consequence of enhanced activity of renin in response to inadequate renal perfusion and hypotension. Most individuals with primary hyperaldosteronism have bilateral adrenal hyperplasia (idiopathic hyperaldosteronism), while only a minority have an aldosterone-producing adenoma (APA; Conn syndrome). Glucocorticoid-suppressible hyperaldosteronism is a rare autosomal dominant condition in which aldosterone is secreted 'ectopically' from the adrenal zonae fasciculata/reticularis in response to ACTH. Rarely, the mineralocorticoid receptor pathway in the distal nephron is activated, even though aldosterone concentrations are low.

Clinical features

Individuals with primary hyperaldosteronism are usually asymptomatic, but may have features of sodium retention or potassium loss. Sodium retention may cause oedema, while hypokalaemia may cause muscle weakness (or even paralysis, especially in South-east Asian populations), polyuria (secondary to renal tubular damage, which produces arginine vasopressin resistance) and occasionally tetany (because of associated metabolic alkalosis and low ionised calcium). Blood pressure is elevated, but accelerated phase hypertension is rare.

Investigations

Biochemical

Routine blood tests may show a hypokalaemic alkalosis. Sodium is usually at the upper end of the reference range in primary hyperaldosteronism, but is characteristically low in secondary hyperaldosteronism (because low plasma volume stimulates arginine vasopressin (antidiuretic hormone, ADH) release and high angiotensin II levels stimulate thirst). The key measurements are plasma renin and aldosterone (see Box 20.45), and in many centres the aldosterone:renin ratio (ARR) is employed as a screening test for primary hyperaldosteronism in hypertensive patients. Almost all antihypertensive drugs interfere with this ratio (β-blockers inhibit, while diuretics stimulate renin secretion). Thus, individuals with an elevated ARR require further testing after stopping many antihypertensive drugs for at least 4 weeks (although if the ratio is still high despite a patient taking ACE inhibitors or angiotensin receptor–blocking drugs then this need not be done as these agents would normally cause a lowering of the ratio). If necessary, antihypertensive agents that have minimal effects on the renin–angiotensin system, such as calcium antagonists and α-blockers, may be substituted. Oral potassium supplementation may also be required, as hypokalaemia itself suppresses renin activity. If, on repeat testing, plasma renin is low and aldosterone concentrations are elevated, then further investigation under specialist supervision may include saline or fludrocortisone suppression tests.

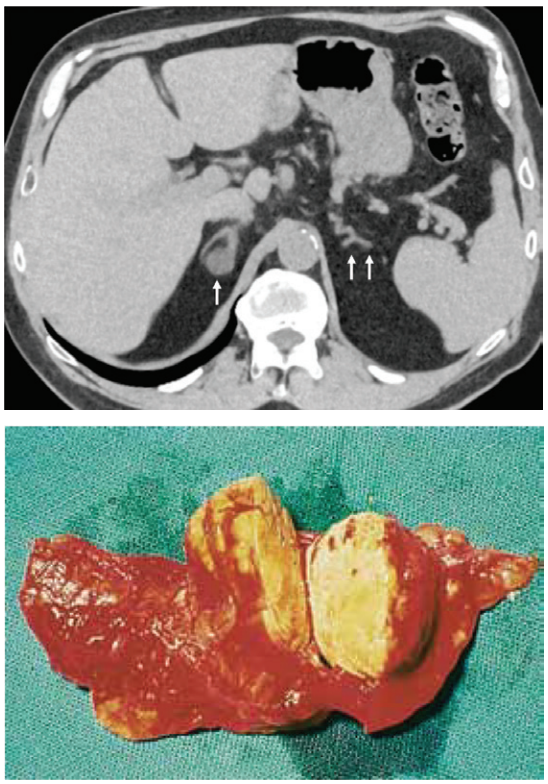

Fig. 20.23 Aldosterone-producing adenoma causing Conn syndrome. A CT scan demonstrating a low attenuation nodule in relation to the medial limb of the right adrenal gland (single arrow) consistent with a lipid-rich adenoma. The left adrenal gland is normal (double arrow). B The tumour is 'canary yellow' because of intracellular lipid accumulation.

Imaging and localisation

Imaging with CT or MRI will identify most APAs (Fig. 20.23A), but it is important to recognise the risk of false positives (non-functioning adrenal adenomas are common) and false negatives (imaging may have insufficient resolution to identify adenomas with a diameter of less than 0.5 cm). If the imaging is inconclusive and there is an intention to proceed with surgery on the basis of strong biochemical evidence of an APA, then adrenal vein catheterisation with measurement of aldosterone (and cortisol to confirm positioning of the catheters) is usually required. In some centres, this is performed even in the presence of a unilateral 'adenoma' in patients aged > 30 years, to avoid inadvertent removal of an incidental non-functioning adenoma contralateral to a radiologically inapparent cause of aldosterone excess.

Management

Mineralocorticoid receptor antagonists (spironolactone and eplerenone) are valuable in treating both hypokalaemia and hypertension in all forms of mineralocorticoid excess. Up to 20% of males develop gynaecomastia on spironolactone. Amiloride (10–40 mg/day), which blocks the epithelial sodium channel regulated by aldosterone, is an alternative.

In patients with an APA, medical therapy is usually given for a few weeks to normalise whole-body electrolyte balance before unilateral adrenalectomy. Laparoscopic surgery cures the biochemical abnormality but, depending on the pre-operative duration, hypertension remains in as many as 70% of cases, probably because of irreversible damage to the systemic microcirculation.

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Phaeochromocytoma and paraganglioma

These are rare neuroendocrine tumours that may secrete catecholamines (adrenaline/epinephrine, noradrenaline/norepinephrine). Approximately 80% of these tumours occur in the adrenal medulla (phaeochromocytomas), while 20% arise elsewhere in the body in sympathetic ganglia (paragangliomas). Most are benign, but approximately 15% show malignant features (local invasion or metastases) at presentation or at a later date. Around 40% are associated with inherited disorders, including neurofibromatosis, von Hippel–Lindau syndrome, MEN 2a and MEN 2b. Paragangliomas are particularly associated with pathogenic variants in the succinate dehydrogenase (SDH) A, B, C and D genes. Other genetic causes include pathogenic variants in *SDHAF2*, *TMEN127* and *MAX*.

Clinical features

These depend on the pattern of catecholamine secretion and are listed in Box 20.46.

Some patients present with hypertension, although it has been estimated that phaeochromocytoma accounts for less than 0.1% of cases of hypertension. The presentation may be with a complication of hypertension, such as stroke, myocardial infarction, left ventricular failure, hypertensive retinopathy or accelerated phase hypertension. The apparent paradox of postural hypotension between episodes is explained by 'pressure natriuresis' during hypertensive episodes so that intravascular volume is reduced. There may also be features of the familial syndromes associated with phaeochromocytoma. Paragangliomas are often non-functioning.

Investigations

Excessive secretion of catecholamines can be confirmed by measuring metabolites in plasma and/or urine (metanephrine and normetanephrine). There is a high 'false-positive' rate, as elevated metanephrine concentrations may be seen in stressed patients (during acute illness, following vigorous exercise or severe pain) and following ingestion of some drugs such as tricyclic antidepressants. For this reason, a repeat sample should usually be requested if elevated levels are found, although, as a rule, the higher the concentration of metanephrines, the more likely the diagnosis of phaeochromocytoma/paraganglioma. Serum chromogranin A may be a useful tumour marker in patients with non-secretory tumours and/or metastatic disease. 3-methoxytyramine (3-MT) is a dopamine metabolite, which may be elevated in head and neck paragangliomas and in paragangliomas with a greater propensity to metastasise, especially those associated with SDH B paraganglioma syndrome. Genetic testing should be considered in all individuals with phaeochromocytoma/paraganglioma.

20.46 Clinical features of phaeochromocytoma/functional paraganglioma

- Hypertension (usually paroxysmal; often postural drop of blood pressure)
- Paroxysms of:
  - Pallor (occasionally flushing)
  - Palpitations, sweating
  - Headache
  - Anxiety (angor animi)
- Abdominal pain, vomiting
- Constipation
- Weight loss
- Glucose intolerance

Localisation

Phaeochromocytomas are usually identified by abdominal CT or MRI (Fig. 20.24). Localisation of paragangliomas may be more difficult. Scintigraphy using meta-iodobenzyl guanidine (MIBG) can be useful, particularly if combined with CT, for adrenal phaeochromocytoma, but is often negative in paraganglioma. ^{18}F-deoxyglucose PET or gallium-68 (^{68}Ga)-DOTANOC or DOTATATE PET-CT are especially useful for detection of malignant disease and for confirming an imaging abnormality as a paraganglioma in an individual with underlying risk due to a genetic syndrome.

Management

In functioning tumours, medical therapy is required to prepare the patient for surgery, preferably for a minimum of 6 weeks, to allow restoration of normal plasma volume. Traditionally the non-competitive α-blocker phenoxybenzamine (10–20 mg orally 3–4 times daily) is used, but competitive α-blockers, such as doxazosin, provide equally effective preparation with fewer side-effects. If α-blockade produces a marked tachycardia, then a β-blocker such as propranolol can be added. On no account should a β-blocker be given before an α-blocker, as this may cause a paradoxical rise in blood pressure due to unopposed α-mediated vasoconstriction.

During surgery, intravenous sodium nitroprusside, magnesium and the short-acting α-antagonist phentolamine are useful in controlling hypertensive episodes, which may result from anaesthetic induction or tumour mobilisation. Post-operative hypotension may occur and require volume expansion and, very occasionally, noradrenaline (norepinephrine) infusion, but is uncommon if the patient has been adequately prepared.

Metastatic tumours may behave in an aggressive or a very indolent fashion. Management options include debulking surgery, radionuclide therapy with ^{131}I MIBG or lutetium-177 (^{177}Lu)-DOTATATE, chemotherapy and (chemo)embolisation of hepatic metastases; some may respond to tyrosine kinase and angiogenesis inhibitors.

Congenital adrenal hyperplasia

Pathophysiology and clinical features

Inherited defects in enzymes of the cortisol biosynthetic pathway (see Fig. 20.20) result in insufficiency of hormones downstream of the block, with impaired negative feedback and increased ACTH secretion. ACTH

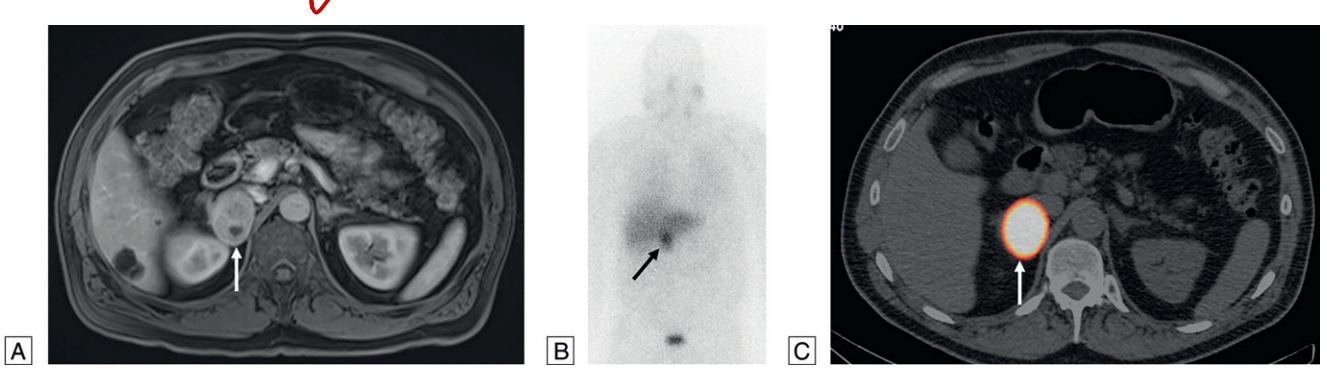

Fig. 20.24 A Contrast-enhanced MRI demonstrating a 5 cm right adrenal mass (arrow) consistent with a phaeochromocytoma. B Planar ^{123}I MIBG scan shows a solitary focus of abnormal MIBG uptake projected over the right upper abdomen (arrow). C SPECT/CT localising the uptake to the right adrenal mass (arrow).

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then stimulates the production of steroids upstream of the enzyme block. This produces adrenal hyperplasia and a combination of clinical features that depend on the severity and site of the defect in biosynthesis. All of these enzyme abnormalities are inherited as autosomal recessive traits.

The most common enzyme defect is 21-hydroxylase deficiency. This results in impaired synthesis of cortisol and aldosterone, and accumulation of 17-OH-progesterone, which is then diverted to form adrenal androgens. In about one-third of cases, this defect is severe and presents in infancy with features of glucocorticoid and mineralocorticoid deficiency (see Box 20.41) and androgen excess, such as ambiguous genitalia in girls. In the other two-thirds, mineralocorticoid secretion is adequate but there may be features of AI and/or ACTH and androgen excess, including precocious pseudo-puberty, which is distinguished from 'true' precocious puberty by low gonadotrophins. Sometimes the mildest enzyme defects are not apparent until adult life, when females may present with amenorrhoea and/or hirsutism. This is called 'non-classical' or 'late-onset' congenital adrenal hyperplasia.

Defects of all the other enzymes in Figure 20.20 are rare. Both 17-hydroxylase and 11β-hydroxylase deficiency may produce hypertension due to excess production of 11-deoxycorticosterone, which has mineralocorticoid activity.

Investigations

Circulating 17-OH-progesterone levels are raised in 21-hydroxylase deficiency, but this may be demonstrated only after ACTH administration (ACTH stimulation test) in late-onset cases. To avoid salt-wasting crises in infancy, 17-OH-progesterone can be routinely measured in heel-prick blood spot samples taken from all infants in the first week of life. Assessment is otherwise as described earlier for AI.

Management

The aim is to replace deficient corticosteroids and to suppress ACTH-driven adrenal androgen production. A careful balance is required between adequate suppression of adrenal androgen excess and excessive glucocorticoid replacement resulting in features of Cushing syndrome. In children, growth velocity is an important measurement, since either under- or over-replacement with glucocorticoids suppresses growth. In adults, there is no uniformly agreed adrenal replacement regimen, and clinical features (menstrual cycle, hirsutism, weight gain, blood pressure) and biochemical profiles (plasma renin, 17-OH-progesterone and testosterone levels) provide a guide.

Women with late-onset 21-hydroxylase deficiency may not require corticosteroid replacement. If hirsutism is the main problem, anti-androgen therapy may be just as effective.

The endocrine pancreas and gastrointestinal tract

A series of hormones are secreted from cells distributed throughout the gastrointestinal tract and pancreas. Functional anatomy and physiology are described in Chapters 22 and 23. Diseases associated with abnormalities of these hormones are listed in Box 20.47. Most are rare, with the exception of diabetes mellitus (Ch. 21).

Presenting problems in endocrine pancreas disease

Hypoglycaemic disorders

Hypoglycaemia most commonly occurs as a side-effect of treatment with insulin or sulphonylurea drugs in people with diabetes mellitus. In non-diabetic individuals, symptomatic hypoglycaemia is rare, but it is not uncommon to detect venous blood glucose concentrations below 3.0 mmol/L (54 mg/dL) in asymptomatic patients. Similarly, the increasingly common use of continuous glucose monitoring systems in non-diabetic individuals identifies apparent 'hypoglycaemia' in a significant proportion of healthy people. For these reasons, and because the symptoms of hypoglycaemia are non-specific, investigation of a potential hypoglycaemic disorder should be pursued only if all three conditions of the Whipple triad are met (Fig. 20.25). There is no specific blood glucose concentration at which hypoglycaemia can be said to occur, although the lower the blood glucose concentration, the more likely it is to have pathological significance. Investigations are unlikely to be needed unless glucose concentrations below 3.0 mmol/L are observed; many patients with true hypoglycaemia demonstrate glucose levels below 2.2 mmol/L (40 mg/dL).

Hypoglycaemia is often precipitated and/or exacerbated by fasting and physical exercise. With the increasing use of bariatric surgery, and more specifically gastric bypass surgery, more patients are presenting with post-prandial hypoglycaemia due to excess stimulated insulin secretion due to the rapid carbohydrate loads being delivered directly to the small intestine.

Clinical assessment

The clinical features of hypoglycaemia are described in the section on insulin-induced hypoglycaemia in Chapter 21. Individuals with chronic

i 20.47 Classification of endocrine diseases of the pancreas and gastrointestinal tract

	Primary	Secondary
Hormone excess	Insulinoma Gastrinoma (Zollinger–Ellison syndrome) Carcinoid syndrome (secretion of 5-HT) Glucagonoma VIPoma Somatostatinoma	Hypergastrinaemia of achlorhydria Hyperinsulinaemia after bariatric surgery
Hormone deficiency	Diabetes mellitus	
Hormone resistance	Insulin resistance syndromes (e.g. type 2 diabetes mellitus, lipodystrophy, Donohue syndrome)	
Non-functioning tumours	Pancreatic carcinoma Pancreatic neuroendocrine tumour	

(5-HT = 5-hydroxytryptamine, serotonin)

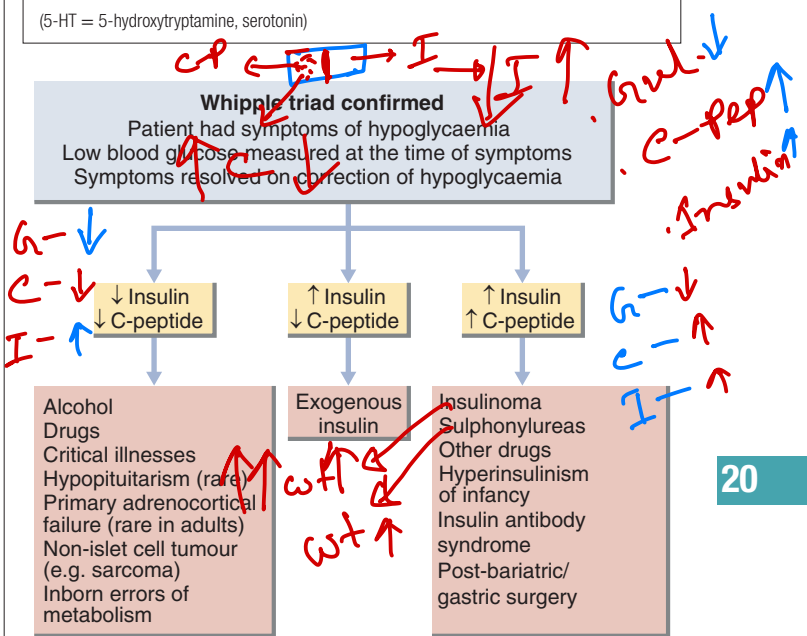

Fig. 20.25 Differential diagnosis of hypoglycaemic disorders. Measurement of insulin and C-peptide concentrations during an episode is helpful in determining the underlying cause.

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hypoglycaemic disorders often have attenuated autonomic responses and 'impaired awareness of hypoglycaemia', and may present with a wide variety of features of neuroglycopenia, including odd behaviour and convulsions. The symptoms are usually episodic and relieved by consumption of carbohydrate. Hypoglycaemia should be considered in all comatose patients, even if there is an apparently obvious cause, such as hemiplegic stroke or alcohol intoxication.

Investigations

Does the patient have a hypoglycaemic disorder?

Patients who present acutely with delirium, coma, convulsions or stroke should be tested for hypoglycaemia at the bedside with a capillary blood glucose sample. While this is sufficient to exclude hypoglycaemia, blood glucose meters are relatively inaccurate in the hypoglycaemic range and the diagnosis should always be confirmed by a laboratory-based glucose measurement. At the same time, a sample should be taken for later measurement of alcohol, insulin, C-peptide, cortisol and sulphonylurea levels, if hypoglycaemia is confirmed. Taking these samples during an acute presentation prevents subsequent unnecessary dynamic tests and is of medico-legal importance in cases where poisoning is suspected.

Patients who attend the outpatient clinic with episodic symptoms suggestive of hypoglycaemia present a more challenging problem. The gold standard diagnostic test is the prolonged (72-hour) fast. If symptoms of hypoglycaemia develop during the fast, then blood samples should be taken to confirm hypoglycaemia and for measurement of insulin and C-peptide. Hypoglycaemia is then corrected with oral or intravenous glucose and the Whipple triad completed by confirmation of the resolution of symptoms. A mixed meal tolerance test may be undertaken in suspected post-prandial hypoglycaemia.

What is the cause of the hypoglycaemia?

In the acute setting, the underlying diagnosis is often obvious. In non-diabetic individuals, alcohol excess is the most common cause of hypoglycaemia in the UK, but other drugs – e.g. salicylates, quinine and pentamidine – may also be implicated. Hypoglycaemia is one of many metabolic derangements that occur in patients with hepatic failure, renal failure, adrenal insufficiency, sepsis or malaria.

Hypoglycaemia in the absence of insulin, or any insulin-like factor, in the blood indicates impaired gluconeogenesis and/or availability of glucose from glycogen in the liver. Hypoglycaemia associated with high insulin and low C-peptide concentrations is indicative of administration of exogenous insulin, either factitiously or feloniously. Adults with high insulin and C-peptide concentrations during an episode of hypoglycaemia are most likely to have an insulinoma, but insulin antibody syndrome and sulphonylurea ingestion should also be considered (the latter particularly in individuals with access to such medication, such as health-care professionals or family members of someone with type 2 diabetes). Individuals with post-prandial hypoglycaemia following bariatric/gastric surgery will also have elevated insulin and C-peptide concentrations, but the diagnosis is usually obvious from the history. Suppressed plasma β-hydroxybutyrate helps confirm inappropriate insulin secretion during fasting. Usually, insulinomas in the pancreas are small (<10 mm diameter) but can be identified by CT, MRI or ultrasound (endoscopic or laparoscopic). Imaging should include the liver since around 10% of insulinomas are malignant and may metastasise to the liver. Rarely, large non-pancreatic tumours, such as sarcomas, may cause recurrent hypoglycaemia because of their ability to produce excess pro-insulin-like growth factor-2 (pro-IGF-2), which has considerable structural homology to insulin.

Management

Treatment of acute hypoglycaemia should be initiated as soon as laboratory blood samples have been taken and should *not* be deferred until formal laboratory confirmation has been obtained. Intravenous dextrose (5% or 10%) is effective in the short term in the obtunded patient and should be followed on recovery with oral unrefined carbohydrate (starch). Continuous dextrose infusion may be necessary, especially in sulphonylurea poisoning. Intramuscular glucagon (1 mg) stimulates hepatic glucose release but is ineffective in patients with depleted glycogen reserves, such as in alcohol excess or liver disease.

Chronic recurrent hypoglycaemia in insulin-secreting tumours can be treated by regular consumption of oral carbohydrate combined with agents that inhibit insulin secretion (diazoxide or somatostatin analogues). Insulinomas are resected when benign, providing the individual is fit enough to undergo surgery. Metastatic malignant insulinomas may be incurable and are managed along the same lines as other metastatic neuroendocrine tumours (see below). Insulin antibody syndrome may settle spontaneously after a few months, but immunosuppressive therapy with glucocorticoids and biologics (such as rituximab) may be required.

Gastroenteropancreatic neuroendocrine tumours

Neuroendocrine tumours (NETs) are a heterogeneous group derived from neuroendocrine cells in many organs, including the gastrointestinal tract, lung, adrenals (phaeochromocytoma) and thyroid (medullary carcinoma). Most NETs occur sporadically but a proportion are associated with genetic cancer syndromes, such as MEN 1, 2a and 2b, and neurofibromatosis type 1. NETs may secrete hormones into the circulation.

Gastroenteropancreatic NETs arise in organs that are derived embryologically from the gastrointestinal tract. Most commonly, they occur in the small bowel but they can also arise elsewhere in the bowel, pancreas, thymus and bronchi. The term 'carcinoid' is often used when referring to non-pancreatic gastrointestinal NETs because, when initially described, they were thought to behave in an indolent fashion compared with conventional cancers. It is now recognised that there is a wide spectrum of malignant potential for all NETs; some are more usually benign (most insulinomas and appendiceal carcinoid tumours), while others have an aggressive clinical course with widespread metastases (small-cell carcinoma of the lung). The majority of gastroenteropancreatic NETs behave in an intermediate manner, with relatively slow growth but a propensity to invade and metastasise to remote organs, especially the liver.

Clinical features

Patients with gastroenteropancreatic NETs often have a history of abdominal pain over many years prior to diagnosis and usually present with local mass effects, such as small-bowel obstruction, appendicitis and pain from hepatic metastases. Thymic and bronchial carcinoids occasionally present with ectopic ACTH syndrome. Pancreatic NETs can also cause hormone excess (Box 20.48) but most are non-functional. The classic 'carcinoid syndrome' (Box 20.49) occurs when vasoactive hormones reach the

20.48 Pancreatic neuroendocrine tumours

Tumour	Hormone	Effects
Gastrinoma	Gastrin	Peptic ulcer and steatorrhoea (Zollinger–Ellison syndrome)
Insulinoma	Insulin	Recurrent hypoglycaemia (see above)
VIPoma	Vasoactive intestinal peptide (VIP)	Watery diarrhoea and hypokalaemia
Glucagonoma	Glucagon	Diabetes mellitus, necrolytic migratory erythema
Somatostatinoma	Somatostatin	Diabetes mellitus and steatorrhoea

20.49 Clinical features of the carcinoid syndrome

- Episodic flushing, wheezing and diarrhoea
- Facial telangiectasia
- Cardiac involvement (tricuspid regurgitation, pulmonary stenosis, right ventricular endocardial plaques) leading to heart failure

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systemic circulation. In the case of gastrointestinal carcinoids, this invariably means that the tumour has metastasised to the liver or there are peritoneal deposits, which allow secreted hormones to gain access to the systemic circulation; hormones secreted by the primary tumour into the portal vein are metabolised and inactivated in the liver. The features of Zollinger–Ellison syndrome are described on page 834.

Investigations

A combination of ultrasound, CT, MRI and/or functional imaging (Fig. 20.26) will usually identify the primary tumour and allow staging, which is crucial for determining prognosis. Biopsy of the primary tumour or a metastatic deposit is required to confirm the histological type. NETs demonstrate immunohistochemical staining for the proteins chromogranin A and synaptophysin, and the histological grade provides important prognostic information: the higher the Ki67 proliferation index, the worse the prognosis.

Carcinoid syndrome is confirmed by measuring elevated concentrations of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, in a 24-hour urine collection. False positives can occur, particularly if the individual has been eating serotonin-rich foods, such as avocado and pineapple. Plasma chromogranin A can be measured in a fasting blood sample, along with the hormones listed in Box 20.48. All of these can be useful as tumour markers.

Management

Treatment of solitary tumours is by surgical resection. If metastatic or multifocal primary disease is present, then surgery is usually not indicated, unless there is a complication such as gastrointestinal obstruction. Diazoxide can reduce insulin secretion in insulinomas, and high doses of proton pump inhibitors suppress acid production in gastrinomas. Somatostatin analogues are effective in reducing the symptoms of carcinoid syndrome and of excess glucagon and vasoactive intestinal peptide (VIP) production. The slow-growing nature of NETs means that conventional cancer therapies, such as chemotherapy and radiotherapy, have limited efficacy, but use of somatostatin analogues is associated with improved progression-free survival, and ^{177}Lu-DOTATATE is indicated for many patients with further disease progression. Other treatments, such as resection/embolisation/ablation of hepatic metastases, may have a role in the palliation of symptoms, but debate exists as to whether this prolongs life. The tyrosine kinase inhibitor sunitinib and the mammalian target of rapamycin (mTOR) inhibitor everolimus have shown significant improvements in progression-free survival in patients with advanced and progressive pancreatic and lung NETs that are not poorly differentiated.

The hypothalamus and the pituitary gland

Diseases of the hypothalamus and pituitary have an annual incidence of approximately 3:100 000 and a prevalence of 30–70 per 100 000. The pituitary plays a central role in several major endocrine axes, so that investigation and treatment invariably involve several other endocrine glands.

Functional anatomy, physiology and investigations

The anatomical relationships of the pituitary are shown in Figure 20.27 and its numerous functions are shown in Figure 20.2. The pituitary gland is enclosed in the sella turcica and bridged over by a fold of dura mater called the diaphragma sellae, with the sphenoidal air sinuses below and the optic chiasm above. The cavernous sinuses are lateral

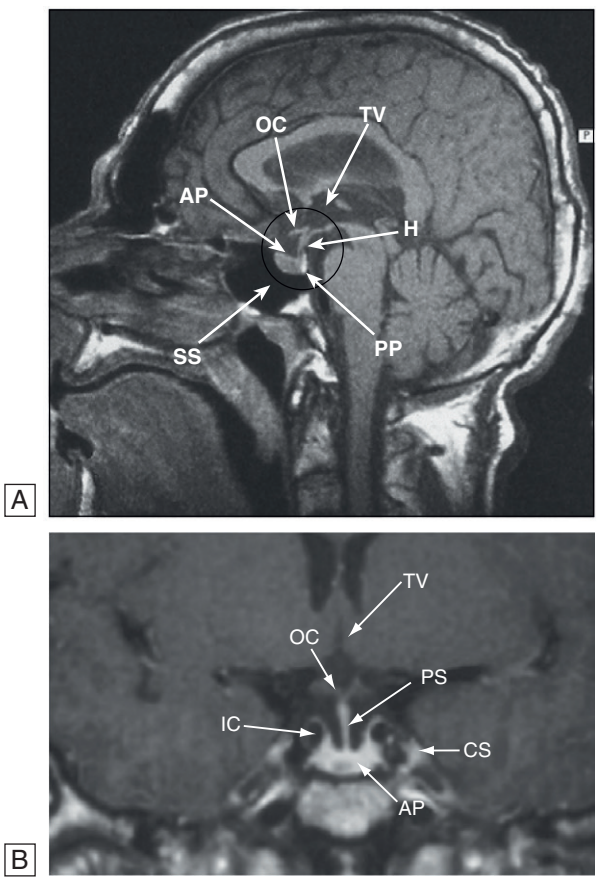

Fig. 20.27 Anatomical relationships of the normal pituitary gland and hypothalamus. See also Fig. 20.2. A Sagittal MRI. B Coronal MRI. (AP = anterior pituitary; CS = cavernous sinus; H = hypothalamus; IC = internal carotid artery; OC = optic chiasm; PP = posterior pituitary; PS = pituitary stalk; SS = sphenoid sinus; TV = third ventricle)

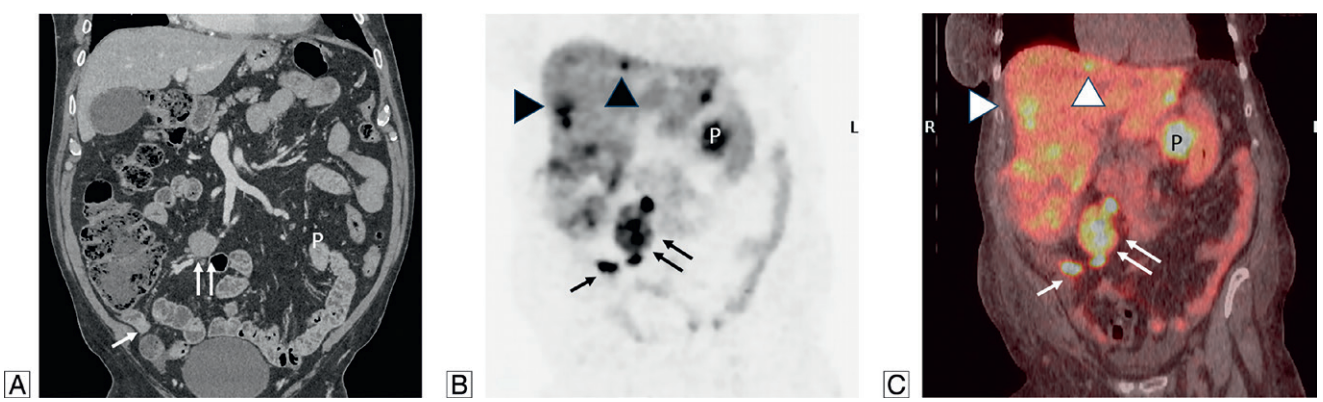

Fig. 20.26 Patient with metastatic small bowel carcinoid. A Coronal contrast-enhanced CT demonstrates a small enhancing tumour in the terminal ileum (single arrow) with metastatic mesenteric lymph nodes (double arrows). B and C Corresponding uptake seen on the staging ^{68}Ga-DOTATOC PET-CT scans, which also demonstrate liver metastases (arrowheads) and a pancreatic metastasis (P) not seen on the initial CT scan.

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20.50 Classification of diseases of the pituitary and hypothalamus

	Primary	Secondary
Non-functioning tumours	Pituitary adenoma Craniopharyngioma Metastatic tumours	
Hormone excess	Prolactinoma Acromegaly Cushing disease Rare TSH-, LH- and FSH-secreting adenomas Syndrome of inappropriate antidiuretic hormone (SIADH, p. 666)	Disconnection hyperprolactinaemia
Hormone deficiency	Hypopituitarism AVP deficiency (cranial diabetes insipidus)	GnRH deficiency (Kallmann syndrome)
Hormone resistance	Growth hormone resistance (Laron dwarfism) AVP resistance (nephrogenic diabetes insipidus)	

(FSH = follicle-stimulating hormone; GnRH = gonadotrophin-releasing hormone; LH = luteinising hormone; TSH = thyroid-stimulating hormone)

20.51 How to investigate patients with suspected pituitary or hypothalamic disease

Identify pituitary hormone deficiency

ACTH deficiency
- ACTH stimulation test (see Box 20.42)
- Insulin tolerance test (see Box 20.55): only if there is uncertainty in interpretation of ACTH stimulation test (e.g. acute presentation)

LH/FSH deficiency
- In the male, measure random serum testosterone, LH and FSH
- In the pre-menopausal female, ask if the menses are regular
- In the post-menopausal female, measure random serum LH and FSH (FSH normally > 30 IU/L and LH > 20 IU/L)

TSH deficiency
- Measure random serum T4
- Note that TSH is often detectable in secondary hypothyroidism

Growth hormone deficiency

Only investigate if growth hormone replacement therapy is being contemplated
- Measure immediately after exercise
- Consider other stimulatory tests (see Box 20.54)

AVP deficiency (cranial diabetes insipidus)

Only investigate if patient complains of polyuria/polydipsia, which may be masked by ACTH or TSH deficiency
- Exclude other causes of polyuria with blood glucose, potassium and calcium measurements
- 3% saline infusion test or water deprivation test

Identify hormone excess
- Measure random serum prolactin
- Investigate for acromegaly (glucose tolerance test) or Cushing syndrome if there are clinical features

Establish the anatomy and diagnosis
- Consider visual field testing
- Image the pituitary and hypothalamus by MRI or CT

(ACTH = adrenocorticotrophic hormone; CT = computed tomography; FSH = follicle-stimulating hormone; LH = luteinising hormone; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone)

to the pituitary fossa and contain the 3rd, 4th and 6th cranial nerves and the internal carotid arteries. The gland is composed of two lobes, anterior and posterior, and is connected to the hypothalamus by the infundibular stalk, which has portal vessels carrying blood from the median eminence of the hypothalamus to the anterior lobe and nerve fibres to the posterior lobe.

Diseases of the hypothalamus and pituitary are classified in Box 20.50. By far the most common disorder is an adenoma of the anterior pituitary gland.

Investigation of patients with pituitary disease

Although pituitary disease presents with diverse clinical manifestations (see below), the approach to investigation is similar in all cases (Box 20.51).

The approach to testing for hormone deficiency is outlined in Box 20.51. Details are given in the sections on individual glands elsewhere in this chapter. Tests for hormone excess vary according to the hormone in question. For example, although prolactin secretion rises in response to stress and slightly during sleep, levels are generally steady across the day. Thus, assuming that the patient was not distressed by venepuncture, a random measurement of serum prolactin is usually sufficient to diagnose hyperprolactinaemia. In contrast, growth hormone is secreted in a pulsatile fashion. A high random level does not confirm acromegaly; the diagnosis is confirmed only by failure of growth hormone to be suppressed during an oral glucose tolerance test, with usually a high serum IGF-1. Similarly, in suspected ACTH-dependent Cushing disease, random measurement of plasma cortisol is unreliable and the diagnosis is usually made by a dexamethasone suppression and other tests.

The most common local complication of a large pituitary tumour is compression of the optic pathway. The resulting visual field defect can be documented using a Goldmann perimetry chart or with an automated perimetry method.

MRI reveals 'abnormalities' of the pituitary gland in as many as 10% of 'healthy' middle-aged people. It should therefore be performed only if there is a clear biochemical abnormality or if a patient presents with clinical features of pituitary tumour (see below). A pituitary tumour may be classified as either a macroadenoma (> 10 mm diameter) or a microadenoma (≤ 10 mm diameter).

Surgical biopsy is usually only performed as part of a therapeutic operation. Conventional histology identifies tumours as chromophobe (usually non-functioning), acidophil (typically prolactin- or growth hormone–secreting) or basophil (typically ACTH-secreting); immunohistochemistry may confirm their secretory capacity but is poorly predictive of growth potential of the tumour.

Presenting problems in hypothalamic and pituitary disease

The clinical features of pituitary disease are shown in Figure 20.28. Younger women with pituitary disease most commonly present with secondary amenorrhoea or galactorrhoea (in hyperprolactinaemia). Post-menopausal women and men of any age are less likely to report symptoms of hypogonadism and so are more likely to present late with larger tumours causing visual field defects. The presentation and management of pituitary and hypothalamic disease may be affected by old age (Box 20.52). Nowadays, many patients present with an incidental finding of a pituitary tumour on a CT or MRI scan.

Hypopituitarism

Hypopituitarism describes combined deficiency of any of the anterior pituitary hormones. The clinical presentation is variable and depends on the underlying lesion and the pattern of resulting hormone deficiency. The most common cause is a pituitary macroadenoma but other causes are listed in Box 20.53.

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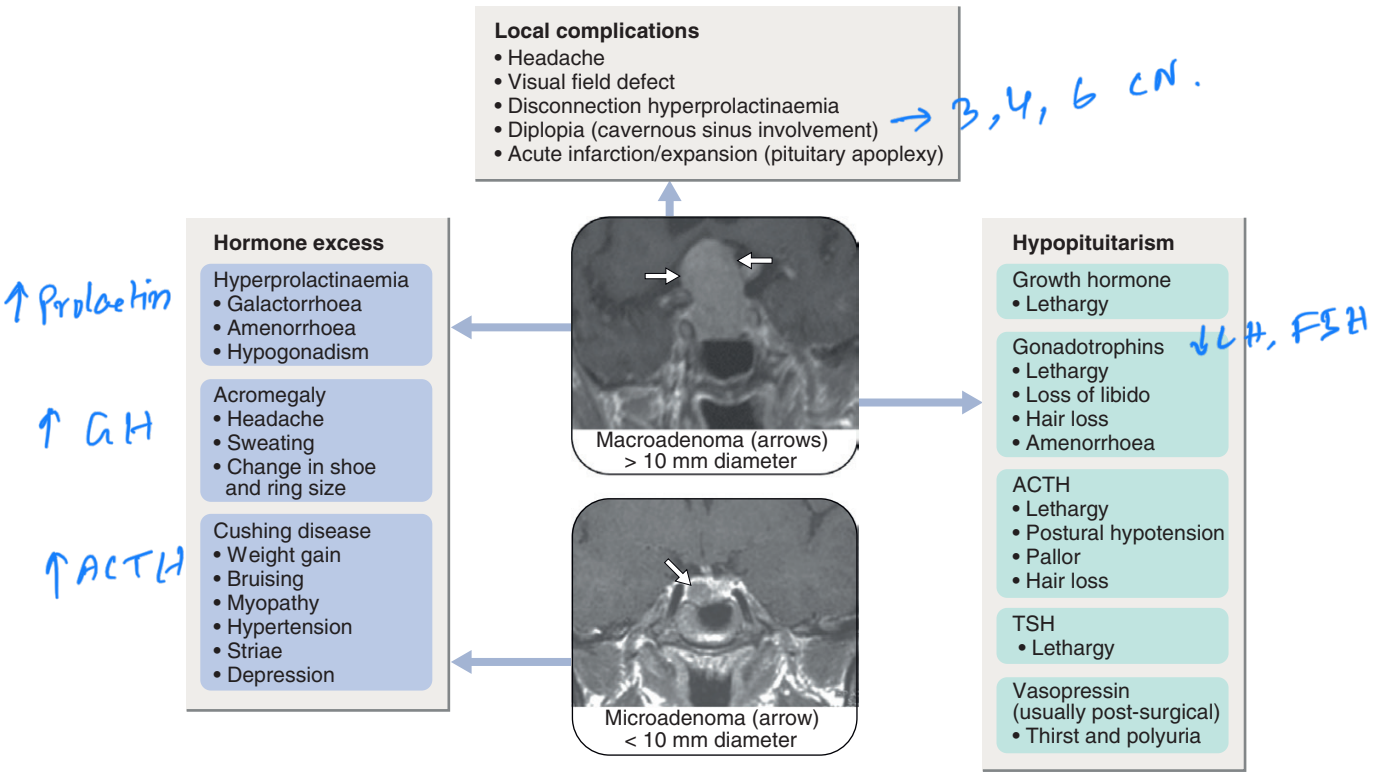

Fig. 20.28 Common symptoms and signs to consider in a patient with suspected pituitary disease. (ACTH = adrenocorticotrophic hormone; TSH = thyroid-stimulating hormone)

20.52 The pituitary and hypothalamus in old age

- **Late presentation**: often with large tumours causing visual disturbance, because early symptoms such as amenorrhoea and sexual dysfunction do not occur or are not recognised.
- **Coincidentally discovered pituitary tumours**: may not require surgical intervention if the visual apparatus is not involved, because of slow growth.
- **Hyperprolactinaemia**: less impact in post-menopausal women who are already 'physiologically' hypogonadal. Macroprolactinomas, however, require treatment because of their potential to cause mass effects.

20.53 Causes of anterior pituitary hormone deficiency

Structural

- Primary pituitary tumour
  - Adenoma*
  - Carcinoma (exceptionally rare)
- Craniopharyngioma*
- Meningioma*
- Secondary tumour (including leukaemia and lymphoma)
- Chordoma
- Germinoma (pinealoma)
- Arachnoid cyst
- Rathke cleft cyst
- Haemorrhage (apoplexy)

Inflammatory/infiltrative

- Sarcoidosis
- Infections, e.g. pituitary abscess, tuberculosis, syphilis, encephalitis
- Lymphocytic hypophysitis
- Haemochromatosis
- Langerhans cell histiocytosis

Congenital deficiencies

- GnRH (Kallmann syndrome)*
- GHRH*
- TRH
- CRH

Functional*

- Chronic systemic illness
- Anorexia nervosa
- Excessive exercise

Other

- Head injury*
- (Para)sellar surgery*
- (Para)sellar radiotherapy*
- Post-partum necrosis (Sheehan syndrome)
- Opioid analgesia

*The most common causes of pituitary hormone deficiency.
(CRH = corticotrophin-releasing hormone; GHRH = growth hormone–releasing hormone; GnRH = gonadotrophin-releasing hormone; TRH = thyrotrophin-releasing hormone)

Clinical assessment

The presentation is highly variable. For example, following radiotherapy to the pituitary region, there is a characteristic sequence of loss of pituitary hormone secretion. Growth hormone secretion is often the earliest to be lost. In adults, this produces lethargy, muscle weakness and increased fat mass, but these features are not obvious in isolation. Next, gonadotrophin (LH and FSH) secretion becomes impaired with loss of libido in the male and oligomenorrhoea or amenorrhoea in the female. Later, in the male there may be gynaecomastia and decreased frequency of shaving. In both sexes, axillary and pubic hair eventually become sparse or even absent and the skin becomes characteristically finer and wrinkled. Chronic anaemia may also occur. The next hormone to be lost is usually ACTH, resulting in symptoms of cortisol insufficiency (including postural hypotension and a *dilutional* hyponatraemia). In contrast to primary adrenal insufficiency (AI), angiotensin II–dependent zona glomerulosa function is not lost and hence aldosterone secretion maintains normal plasma potassium. In contrast to the pigmentation of primary AI due to high levels of circulating ACTH acting on the skin melanocytes, a striking degree of pallor is usually present. Finally, TSH secretion is lost with consequent secondary hypothyroidism. This contributes further to apathy and cold intolerance. In contrast to primary hypothyroidism, frank myxoedema is rare, presumably because the thyroid retains some autonomous function. The onset of all the above symptoms is notoriously insidious. However, patients sometimes present acutely unwell with glucocorticoid deficiency. This may be precipitated by a mild infection or injury, or may occur secondary to pituitary apoplexy.

Other features of pituitary disease may be present (see Fig. 20.28).

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Investigations

The strategy for investigation of pituitary disease is described in Box 20.51. In acutely unwell patients, the priority is to diagnose and treat cortisol deficiency. Other tests can be undertaken later. Specific dynamic tests for diagnosing hormone deficiency are described in Box 20.42 and Box 20.54. More specialised biochemical tests, such as insulin tolerance tests (Box 20.55), GnRH and TRH tests, are rarely required. All patients with biochemical evidence of pituitary hormone deficiency should have an MRI or CT scan to identify pituitary or hypothalamic tumours. If a tumour is not identified, then further investigations are indicated to exclude infectious or infiltrative causes.

Management

Treatment of acutely ill patients is similar to that described for AI, except that sodium depletion is less likely to be present as there is still mineralocorticoid activity due to the renin–angiotensin–aldosterone system (which is lost in primary adrenal insufficiency). Chronic hormone replacement therapies are described below. Once the cause of hypopituitarism is established, specific treatment – of a pituitary macroadenoma, for example (see below) – may be required.

Cortisol replacement

Hydrocortisone should be given if there is ACTH deficiency. Suitable doses are described in the section on adrenal disease on page 722. Mineralocorticoid replacement is not required.

20.54 Tests of growth hormone secretion

GH levels are commonly undetectable, so a choice from the range of 'stimulation' tests is required:

- Insulin-induced hypoglycaemia
- Macimorelin
- Arginine (may be combined with GHRH)
- Glucagon
- Clonidine (in children)

20.55 How and when to do an insulin tolerance test

Use

- Assessment of the HPA axis
- Assessment of GH deficiency
- Indicated when there is doubt after the other tests in Box 20.51
- Usually performed in specialist centres, especially in children
- IV glucose and hydrocortisone must be available for resuscitation

Contraindications

- Ischaemic heart disease
- Epilepsy
- Severe hypopituitarism (0800 hrs plasma cortisol < 180 nmol/L (6.6 μg/dL))

Dose

- 0.15 U/kg body weight soluble insulin IV

Aim

- To produce adequate hypoglycaemia (tachycardia and sweating with blood glucose < 2.2 mmol/L (40 mg/dL))

Blood samples

- 0, 30, 45, 60, 90, 120 mins for blood glucose, plasma cortisol and growth hormone

Results

- Normal subjects: GH > 6.7 μg/L (20 mIU/L)*
- Normal subjects: cortisol > 500 nmol/L (approximately 20.2 μg/dL)*

*The precise cut-off figure for a satisfactory cortisol and GH response depends on the assay used and so varies between centres.
(GH = growth hormone; HPA = hypothalamic–pituitary–adrenal; IV = intravenous)

Thyroid hormone replacement

Levothyroxine 50–150 μg once daily should be given as described on page 700. Unlike in primary hypothyroidism, measuring TSH is not helpful in adjusting the replacement dose because patients with hypopituitarism often secrete glycoproteins that are measured in the TSH assays but are not bioactive. The aim is to maintain serum T4 in the upper part of the reference range. It is dangerous to give thyroid replacement in AI without first giving glucocorticoid therapy, since this may precipitate adrenal crisis.

Sex hormone replacement

This is indicated if there is gonadotrophin deficiency in women under the age of 50 and in men to restore normal sexual function and to prevent osteoporosis.

Growth hormone replacement

Growth hormone (GH) is administered by daily subcutaneous self-injection to children and adolescents with GH deficiency and, until recently, was discontinued once the epiphyses had fused. However, although hypopituitary adults receiving 'full' replacement with hydrocortisone, levothyroxine and sex steroids are usually much improved by these therapies, some individuals remain lethargic and unwell compared with a healthy population. Some of these patients feel better, and have objective improvements in their fat:muscle mass ratio and other metabolic parameters, if they are also given GH replacement. Treatment with GH may also help young adults to achieve a higher peak bone mineral density. The principal side-effect is sodium retention, manifest as peripheral oedema or carpal tunnel syndrome if given in excess. For this reason, GH replacement should be started at a low dose, with monitoring of the response by measurement of serum IGF-1.

Pituitary tumour

Pituitary tumours produce a variety of mass effects, depending on their size and location, but also present as incidental findings on CT or MRI, or with hypopituitarism, as described above. A wide variety of disorders can present as mass lesions in or around the pituitary gland (see Box 20.53). Most intrasellar tumours are pituitary macroadenomas (most commonly non-functioning adenomas; see Fig. 20.28), whereas suprasellar masses may be craniopharyngiomas (see Fig. 20.31). The most common cause of a parasellar mass is a meningioma.

Clinical assessment

Clinical features are shown in Figure 20.28. A common but non-specific presentation is with headache, which may be the consequence of stretching of the diaphragma sellae. Although the classical abnormalities associated with compression of the optic chiasm are bitemporal hemianopia (see Fig. 20.29) or upper quadrantanopia, any type of visual field defect can result from suprasellar extension of a tumour because it may compress the optic nerve (unilateral loss of acuity or scotoma) or the optic tract (homonymous hemianopia). Optic atrophy may be apparent on ophthalmoscopy. Lateral extension of a sellar mass into the cavernous sinus with subsequent compression of the 3rd, 4th or 6th cranial nerve may cause diplopia and strabismus, but in anterior pituitary tumours this is an unusual presentation.

Occasionally, pituitary tumours infarct or there is bleeding into cystic lesions. This is termed 'pituitary apoplexy' and may result in sudden expansion with local compression symptoms and acute-onset hypopituitarism. Non-haemorrhagic infarction can also occur in a normal pituitary gland; predisposing factors include catastrophic obstetric haemorrhage (Sheehan syndrome), diabetes mellitus and raised intracranial pressure.

Investigations

Patients suspected of having a pituitary tumour should undergo MRI. If MRI is not available, CT may be used but is inferior for assessment of pituitary disease and will not show the majority of small pituitary tumours. For patients intolerant of MRI, this investigation may be performed under general anaesthaesia if needed, or imaging performed by CT. While some lesions have distinctive neuro-radiological features, the definitive diagnosis is made on histology after surgery. All patients with (para)sellar

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space-occupying lesions should have pituitary function assessed as described in Box 20.51.

Management

Modalities of treatment of common pituitary and hypothalamic tumours are shown in Box 20.56. Associated hypopituitarism should be treated as described above.

Urgent treatment is required if there is evidence of pressure on visual pathways. The chances of recovery of a visual field defect are proportional to the duration of symptoms, with full recovery unlikely if the defect has been present for longer than 4 months. In the presence of a sellar mass lesion, it is crucial that serum prolactin is measured before emergency surgery is performed. If the prolactin is over 5000 mIU/L (236 ng/mL), then the lesion is likely to be a macroprolactinoma and should respond to a dopamine agonist with shrinkage of the lesion, typically making surgery unnecessary (see Fig. 20.29).

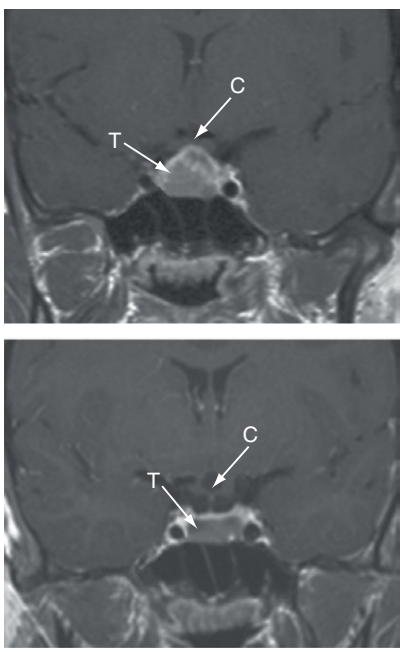

Fig. 20.29 Shrinkage of a macroprolactinoma following treatment with a dopamine agonist. A MRI scan showing a pituitary macroadenoma (T) compressing the optic chiasm (C). B MRI scan of the same tumour following treatment with a dopamine agonist. The macroadenoma, which was a prolactinoma, has decreased in size substantially and is no longer compressing the optic chiasm.

Most operations on the pituitary are performed using the trans-sphenoidal approach via the nostrils, while transfrontal surgery via a craniotomy is occasionally needed for suprasellar tumours. It is uncommon to be able to resect lateral extensions into the cavernous sinuses, although with modern endoscopic techniques this is more feasible. All operations on the pituitary carry a risk of damaging normal endocrine function; this risk increases with the size of the primary lesion.

Pituitary function (see Box 20.51) should be retested 4–6 weeks following surgery, primarily to detect the development of any new hormone deficits. Rarely, the surgical treatment of a sellar lesion can result in recovery of hormone secretion that was deficient pre-operatively.

Following surgery, usually after 3–6 months, imaging should be repeated. If there is a significant residual mass and the histology confirms an anterior pituitary tumour, external beam radiotherapy may be given to reduce the risk of recurrence but the risk:benefit ratio needs careful individualised discussion. Radiotherapy is not useful in patients requiring urgent therapy because it takes many months or years to be effective and there is a risk of acute swelling of the mass. Fractionated radiotherapy carries a life-long risk of hypopituitarism (50%–100% in the first 10 years) and annual pituitary function tests are obligatory. There is also concern that radiotherapy might impair cognitive function, cause vascular changes and even induce primary brain tumours, but these side-effects have not been quantified reliably and are likely to be rare. Stereotactic radiosurgery allows specific targeting of residual disease in a more focused fashion.

Non-functioning tumours should be followed up by repeated imaging at intervals that depend on the size of the lesion and on whether or not radiotherapy has been administered. For smaller lesions that are not causing mass effects, therapeutic surgery may not be indicated and the lesion may simply be monitored by serial neuroimaging without a clear-cut diagnosis having been established.

Hyperprolactinaemia/galactorrhoea

Hyperprolactinaemia is a common abnormality that usually presents with hypogonadism and/or galactorrhoea (lactation in the absence of breastfeeding). Since prolactin stimulates milk secretion but not breast development, galactorrhoea rarely occurs in men and only does so if gynaecomastia has been induced by hypogonadism. The differential diagnosis of hyperprolactinaemia is shown in Box 20.57. Many drugs, especially dopamine antagonists, elevate prolactin concentrations. Pituitary tumours can cause hyperprolactinaemia by directly secreting prolactin (prolactinomas, see below), or by compressing the infundibular stalk and thus interrupting the tonic inhibitory effect of hypothalamic dopamine on prolactin secretion ('disconnection' hyperprolactinaemia).

20

20.56 Therapeutic modalities for functioning and non-functioning hypothalamic and pituitary tumours

	Surgery	Radiotherapy	Medical	Comment
Non-functioning pituitary macroadenoma	1st line	2nd line	–	
Prolactinoma	2nd line	2nd line	1st line Dopamine agonists	Dopamine agonists usually cause macroadenomas to shrink
Acromegaly	1st line	2nd line	2nd line Somatostatin analogues Dopamine agonists GH receptor antagonists	Medical therapy does not reliably cause macroadenomas to shrink Radiotherapy and medical therapy are used in combination for inoperable tumours
Cushing disease	1st line	2nd line	2nd line Steroidogenesis inhibitors Pasireotide	Radiotherapy may take many years to reduce ACTH excess and medical therapies may be used as a bridge. Bilateral adrenalectomy may also be considered if the pituitary tumour is not completely resectable
Craniopharyngioma	1st line	2nd line	–	

(ACTH = adrenocorticotrophic hormone; GH = growth hormone)

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20.57 Causes of hyperprolactinaemia

Physiological

- Stress (e.g. post-seizure, venepuncture)
- Pregnancy
- Lactation
- Nipple stimulation
- Sleep
- Coitus
- Exercise
- Baby crying

Drug-induced

Dopamine antagonists

- Antipsychotics (phenothiazines and butyrophenones)
- Antidepressants
- Antiemetics (e.g. metoclopramide, domperidone)

Dopamine-depleting drugs

- Reserpine
- Methyldopa

Oestrogens

- Oral contraceptive pill

Pathological

Common

- Disconnection hyperprolactinaemia (e.g. non-functioning pituitary macroadenoma)
- Prolactinoma (usually microadenoma)
- Primary hypothyroidism
- Polycystic ovary syndrome

Uncommon

- Pituitary tumour secreting prolactin and growth hormone
- Hypothalamic disease
- Renal failure

Rare

- Chest wall reflex (e.g. post herpes zoster)

Prolactin usually circulates as a free (monomeric) hormone in plasma but, in some individuals, prolactin becomes bound to an IgG antibody. This complex is known as macroprolactin and such patients have macroprolactinaemia (not to be confused with macroprolactinoma, a prolactin-secreting pituitary tumour of more than 1 cm in diameter). Since macroprolactin cannot cross blood-vessel walls to reach prolactin receptors in target tissues, it is of no pathological significance. Some commercial prolactin assays do not distinguish prolactin from macroprolactin and so macroprolactinaemia is a cause of spurious hyperprolactinaemia. Identification of macroprolactin requires gel filtration chromatography or polyethylene glycol precipitation techniques, and one of these tests should be performed in all patients with hyperprolactinaemia if the prolactin assay is known to cross-react.

Clinical assessment

In women, in addition to galactorrhoea, hypogonadism associated with hyperprolactinaemia causes secondary amenorrhoea and anovulation with infertility. Important points in the history include drug use, recent pregnancy and menstrual history. The quantity of milk produced is variable and it may be observed only by manual expression. In men there is decreased libido, reduced shaving frequency and lethargy. Unilateral galactorrhoea may be confused with nipple discharge, and breast examination to exclude malignancy or fibrocystic disease is important. Further assessment should address the features in Figure 20.28.

Investigations

Pregnancy should first be excluded before further investigations are performed in women of child-bearing potential. The upper limit of normal for many assays of serum prolactin is approximately 500 mIU/L (24 ng/mL). In non-pregnant and non-lactating patients, monomeric prolactin concentrations of 500–1000 mIU/L (24–47 ng/mL) are likely to be induced by stress or drugs, and a repeat measurement is indicated (a sample for prolactin taken from an intravenous cannula sited several hours before is helpful in identifying hyperprolactinaemia caused by the stress of venepuncture). Levels between 1000 and 5000 mIU/L (47–236 ng/mL) are likely to be due to drugs, a microprolactinoma or 'disconnection' hyperprolactinaemia. Levels above 5000 mIU/L (236 ng/mL) are highly suggestive of a macroprolactinoma.

Patients with prolactin excess should have tests of gonadal function (p. 709), and T4 and TSH should be measured to exclude primary hypothyroidism causing TRH-induced prolactin excess. Unless the prolactin falls after withdrawal of relevant drug therapy, a serum prolactin consistently above the reference range is an indication for MRI or CT scan of the hypothalamus and pituitary. Patients with a macroadenoma also need tests for hypopituitarism (see Box 20.51).

Management

If possible, the underlying cause should be corrected (e.g. cessation of offending drugs and giving levothyroxine replacement in primary hypothyroidism). If dopamine antagonists are the cause, then dopamine agonist therapy is contraindicated; if gonadal dysfunction is the primary concern, sex steroid replacement therapy may be indicated. Troublesome physiological galactorrhoea can also be treated with dopamine agonists (see Box 20.58). Management of prolactinomas is described below.

Prolactinoma

Most prolactinomas in pre-menopausal women are microadenomas because the symptoms of prolactin excess usually result in early presentation. Prolactin-secreting cells of the anterior pituitary share a common lineage with GH-secreting cells, so occasionally prolactinomas can secrete excess GH and cause acromegaly. In prolactinomas there is a relationship between prolactin concentration and tumour size: the higher the level, the bigger the tumour. Some macroprolactinomas can elevate prolactin concentrations above 100 000 mIU/L (4700 ng/mL). The investigation of prolactinomas is the same as for other pituitary tumours (see above).

Management

As shown in Box 20.56, several therapeutic modalities can be employed in the management of prolactinomas.

Medical

Dopamine agonist drugs are first-line therapy for the majority of patients (Box 20.58). They usually reduce serum prolactin concentrations and cause significant tumour shrinkage after several months of therapy (Fig. 20.29), but visual field defects, if present, may improve within days of first administration. It is possible to withdraw dopamine agonist therapy without recurrence of hyperprolactinaemia after a few years of treatment in some patients with a microadenoma. Also, after the menopause, suppression of prolactin is required in microadenomas only if galactorrhoea is troublesome, since hypogonadism is then physiological and tumour growth unlikely. In patients with macroadenomas, drugs can be withdrawn only after curative surgery or radiotherapy and under close supervision.

Ergot-derived dopamine agonists (bromocriptine and cabergoline) can bind to 5-HT_{2B} receptors in the heart and elsewhere and have been associated with fibrotic reactions, particularly tricuspid valve regurgitation, when used in high doses in patients with Parkinson disease. At the relatively low doses used in prolactinomas, most data suggest that systematic screening for cardiac fibrosis is unnecessary, but if dopamine agonist therapy is prolonged, periodic screening by echocardiography or use of non-ergot agents (quinagolide) may be indicated. Dopamine agonists can affect mood and behaviour, precipitating or worsening depression, psychosis and impulse control disorders (e.g. compulsive gambling), and patients should be warned about these potential side-effects.

Surgery and radiotherapy

Surgical decompression is usually necessary only when a macroprolactinoma has failed to shrink sufficiently with dopamine agonist therapy, and this may be because the tumour has a significant cystic component. Surgery may also be performed in patients who are intolerant of dopamine agonists. Microadenomas can be removed selectively by trans-sphenoidal

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20.38 Dopamine agonist therapy: drugs used to treat prolactinomas

Drug	Oral dose*	Advantages	Disadvantages
Bromocriptine	2.5–15 mg/day 2–3 times daily	Available for parenteral use Short half-life; useful in treating infertility Proven long-term efficacy	Ergotamine-like side-effects (nausea, headache, postural hypotension, constipation) Frequent dosing so poor adherence Rare reports of fibrotic reactions in various tissues
Cabergoline	250–1000 µg/week 2 doses/week	Long-acting, so missed doses less important Reported to have fewer ergotamine-like side-effects	Limited data on safety in pregnancy Associated with cardiac valvular fibrosis in Parkinson disease
Quinagolide	50–150 µg/day Once daily	A non-ergot with few side-effects in patients intolerant of the above	Limited data on safety in pregnancy

*Tolerance develops for the side-effects. All of these agents, especially bromocriptine, must be introduced at low dose and increased slowly. If several doses of bromocriptine are missed, the process must start again.

surgery with a cure rate of about 80%, but recurrence is possible; the cure rate for surgery in macroadenomas is substantially lower.

External beam irradiation may be required for some macroadenomas to prevent regrowth if dopamine agonists are stopped.

Pregnancy

Hyperprolactinaemia often presents with infertility, so dopamine agonist therapy may be followed by pregnancy. Patients with microadenomas should be advised to withdraw dopamine agonist therapy as soon as pregnancy is confirmed. In contrast, macroprolactinomas may enlarge rapidly under oestrogen stimulation and so continued dopamine agonist therapy should be considered. Patients with macroprolactinomas need monitoring of visual fields during pregnancy. All patients should be advised to report headache or visual disturbance promptly.

Acromegaly

Acromegaly is caused by growth hormone (GH) secretion from a pituitary tumour, usually a macroadenoma, and carries an approximate twofold excess mortality when untreated.

Clinical features

If GH hypersecretion occurs before puberty, then the presentation is with gigantism. More commonly, GH excess occurs in adult life and presents with acromegaly. If hypersecretion starts in adolescence and persists into adult life, then the two conditions may be combined. The clinical features are shown in Figure 20.30. The most common complaints are headache and sweating. Additional features include those of any pituitary tumour (see Fig. 20.28).

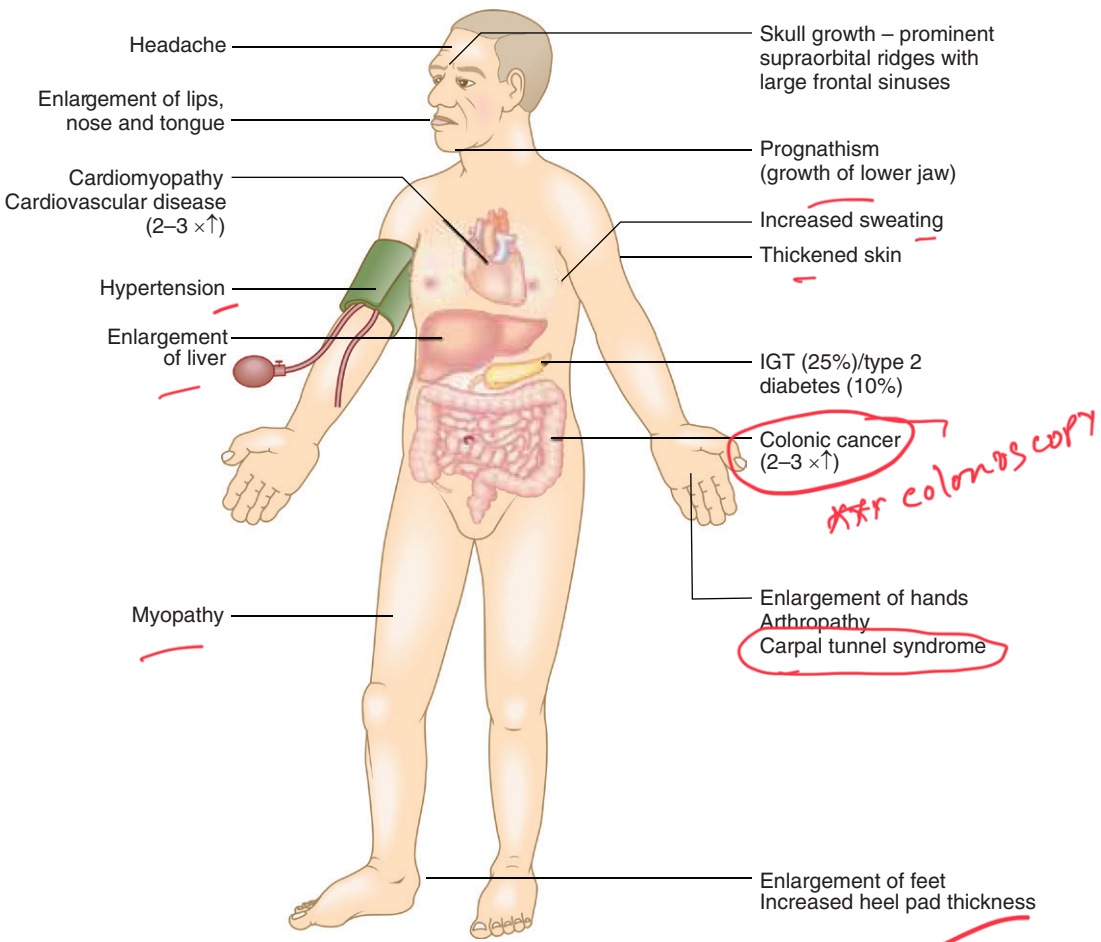

Fig. 20.30 Clinical features of acromegaly. (IGT = impaired glucose tolerance)

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Investigations

The clinical diagnosis must be confirmed by measuring GH levels during an oral glucose tolerance test and measuring serum IGF-1. In normal subjects, plasma GH suppresses to below 0.5 µg/L (approximately 2 mIU/L). In acromegaly, GH does not suppress and in about 30% of patients there is a paradoxical rise; IGF-1 is also elevated. The rest of pituitary function should be investigated as described in Box 20.51. Prolactin concentrations are elevated in about 30% of patients due to co-secretion of prolactin from the tumour. Additional tests in acromegaly may include screening colonoscopy for colonic neoplasms, HbA1c for diabetes and echocardiography for cardiomyopathy.

Management

The main aims are to improve symptoms and to normalise serum GH and IGF-1 to reduce morbidity and mortality. Treatment is summarised in Box 20.56.

Surgical

Trans-sphenoidal surgery is usually the first line of treatment and may result in cure of GH excess, especially in patients with microadenomas. More often, surgery serves to debulk the tumour and further second-line therapy is required, according to post-operative imaging and GH/IGF-1 test results.

Medical

If acromegaly persists after surgery, medical therapy is usually employed to lower GH levels to below 1.0 µg/L (approximately 3 mIU/L) and to normalise IGF-1 concentrations. Medical therapy may be discontinued after several years in patients who have received radiotherapy once the latter has been effective. Somatostatin analogues (such as octreotide, lanreotide or pasireotide) can be administered as slow-release injections every few weeks. Somatostatin analogues can also be used as primary therapy for acromegaly either as an alternative or in advance of surgery, given evidence that they can induce modest tumour shrinkage in some patients. Dopamine agonists are less effective at lowering GH but may sometimes be helpful, especially with associated prolactin excess. Pegvisomant is a peptide GH receptor antagonist administered by daily self-injection and may be indicated in some patients whose GH and IGF-1 concentrations fail to suppress sufficiently following somatostatin analogue therapy.

Radiotherapy

External beam radiotherapy is increasingly employed as third-line treatment if acromegaly persists after surgery, to stop tumour growth and lower GH levels. However, GH levels fall slowly (over many years) and there is a risk of hypopituitarism.

Craniopharyngioma

Craniopharyngiomas are benign tumours that develop in cell rests of the Rathke pouch, and may be located within the sella turcica, or commonly in the suprasellar space. They are often cystic, with a solid component that may or may not be calcified (Fig. 20.31). In young people, they are diagnosed more commonly than pituitary adenomas. They may present with pressure effects on adjacent structures, hypopituitarism and/or AVP deficiency (cranial diabetes insipidus). Other clinical features directly related to hypothalamic damage may also occur. These include hyperphagia and obesity, loss of the sensation of thirst and disturbance of temperature regulation, and these features can be significant clinical challenges to manage.

Craniopharyngiomas often cause considerable morbidity, usually from hypothalamic obesity, water balance problems and/or visual failure. They can be treated by the trans-sphenoidal route, but surgery may also involve a craniotomy, with a relatively high risk of hypothalamic damage and other complications. If the tumour has a large cystic component, it may be safer to place a drain in the cyst cavity that is attached to a subcutaneous access device, rather than attempt a resection. Whatever form it takes, surgery is unlikely to be curative and radiotherapy may often be given to reduce the risk of relapse. Unfortunately, craniopharyngiomas often recur, requiring repeated surgery. The BRAF inhibitor dabrafenib (often in combination with the MEK inhibitor trametinib) has been shown to be highly effective in shrinking craniopharyngiomas with a BRAF V600E mutation. This has been used as a neoadjuvant therapy prior to less invasive surgery or radiotherapy.

Arginine vasopressin deficiency and resistance (diabetes insipidus)

This uncommon disorder is characterised by the persistent excretion of excessive quantities of dilute urine and by thirst. Since 2022, the condition (formerly known as diabetes insipidus) has been renamed as either AVP deficiency or AVP resistance, depending on the underlying aetiology:

- AVP deficiency (cranial diabetes insipidus): there is deficient production of vasopressin by the hypothalamus
- AVP resistance (nephrogenic diabetes insipidus): the renal tubules are unresponsive to vasopressin.

The underlying causes are listed in Box 20.59.

In patients presenting with polyuria–polydipsia syndrome, the other potential diagnosis to be excluded is primary polydipsia, caused by

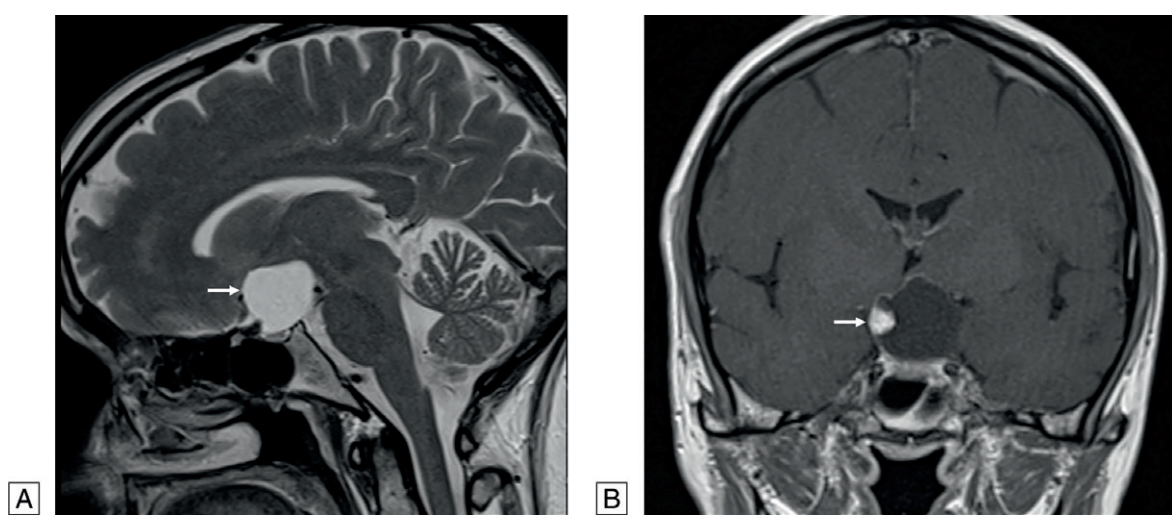

Fig. 20.31 Craniopharyngioma. A Sagittal T2 scan demonstrating a cystic signal suprasellar mass (arrow) indenting the hypothalamus. B The tumour is of corresponding low signal on the post-contrast coronal scan with a right-sided enhancing mural solid nodule (arrow) also noted.

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i 20.59 Causes of AVP deficiency/resistance

AVP deficiency

Structural hypothalamic or high stalk lesion
- See Box 20.53

Idiopathic

Genetic defect
- Dominant (*AVP* mutation)
- Recessive (DIDMOAD syndrome – association of diabetes insipidus with diabetes mellitus, optic atrophy, deafness)

AVP resistance

Genetic defect
- V2 receptor mutation
- Aquaporin-2 mutation
- Cystinosis

Metabolic abnormality
- Hypokalaemia
- Hypercalcaemia

Drug therapy
- Lithium
- Demeclocycline

Poisoning
- Heavy metals

Chronic kidney disease
- Polycystic kidney disease
- Sickle-cell disorder
- Infiltrative disease

drinking excessive amounts of fluid in the absence of a defect in vasopressin or thirst control.

Clinical features

The most marked symptoms are polyuria (> 3 L per 24 hours) and polydipsia. The patient may pass 5–20 L or more of urine in 24 hours. This is of low specific gravity and osmolality. If the patient has an intact thirst mechanism, is conscious and has access to oral fluids, then they can maintain adequate fluid intake. However, in an unconscious patient or a patient with damage to the hypothalamic thirst centre, AVP deficiency/resistance is potentially lethal. If there is associated cortisol deficiency, then AVP deficiency/resistance may not be manifest until glucocorticoid replacement therapy is given.

Investigations

The diagnostic approach to patients with polyuria–polydipsia syndrome is outlined in Figure 20.32.

Measurement of AVP is challenging and not widely available in clinical practice; however, use of copeptin (an osmosensitive surrogate marker of AVP levels) has become routine; either basal or stimulated levels permit differentiation between AVP deficiency, AVP resistance and primary polydipsia. AVP deficiency/resistance is confirmed when the urine is not maximally concentrated (i.e. < 800 mOsmol/kg) in the presence of increased plasma osmolality (i.e. > 300 mOsmol/kg). Sometimes, the diagnosis can be confirmed or refuted by random simultaneous samples of blood and urine, but more often a dynamic test is required. The indirect water deprivation test has, historically, been the investigation of choice in determining the cause of polyuria–polydipsia syndrome.

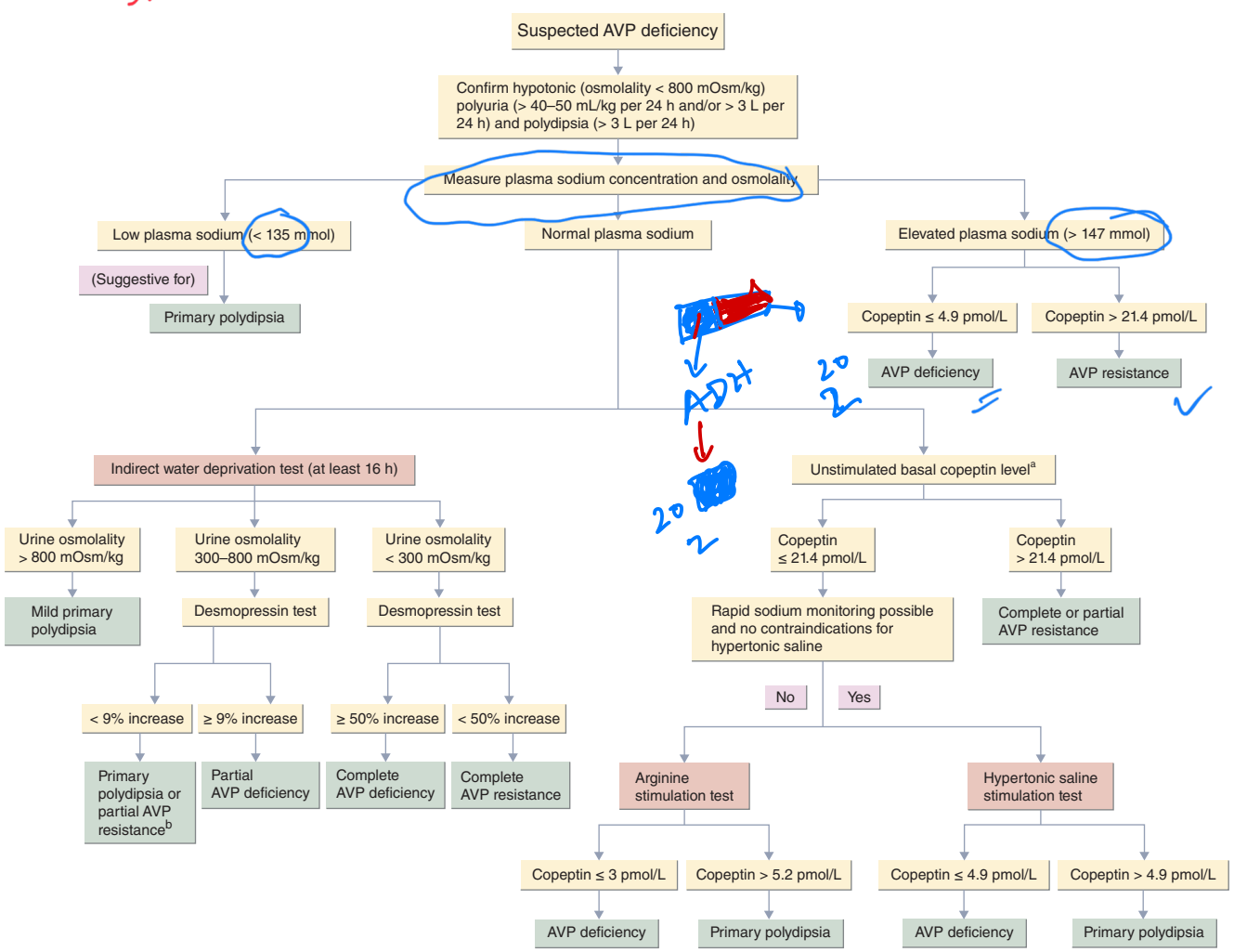

Fig. 20.32 Investigation of suspected AVP deficiency. To convert copeptin from pmol/L to pg/mL, divide by 0.249. [a]Basal copeptin can only be evaluated if no physical or psychological distress and no severe nausea. [b]Plasma osmolality may be required to differentiate between these potential diagnoses. (AVP = arginine vasopressin)

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However, recent evidence attests to the superior diagnostic accuracy of the hypertonic (3%) saline stimulation test (with copeptin measurement). Where hypertonic saline testing is not possible, arginine stimulation testing is an alternative although diagnostic accuracy is lower. Anterior pituitary function and suprasellar anatomy should be assessed in patients with AVP deficiency (see Box 20.51).

In primary polydipsia, the urine may be excessively dilute because of chronic diuresis, which 'washes out' the solute gradient across the loop of Henle, but plasma osmolality is low rather than high. DDAVP (see below) should not be administered to patients with primary polydipsia, since it will prevent excretion of water and there is a risk of severe water intoxication if the patient continues to drink fluid to excess.

In AVP resistance (nephrogenic diabetes insipidus), appropriate further tests may include plasma electrolytes, calcium, ultrasound of the kidneys and urinalysis.

Management

Treatment of AVP deficiency is with 1-deamino-8-D-arginine vasopressin (desmopressin, DDAVP), an analogue of vasopressin that has a longer half-life. For chronic replacement therapy DDAVP may be administered intranasally and orally, although the latter formulation has variable bioavailability. In sick patients, DDAVP should be given by intramuscular injection. The dose of DDAVP should be adjusted on the basis of serum sodium concentrations and/or osmolality. The principal hazard is excessive treatment, resulting in water intoxication and hyponatraemia. Conversely, inadequate treatment results in thirst and polyuria. The ideal dose prevents nocturia and excessive polyuria, but allows a degree of mild polyuria from time to time to allow excretion of excess water (e.g. DDAVP nasal dose 5 µg in the morning and 10 µg at night).

The polyuria in AVP resistance is improved by thiazide diuretics (e.g. bendroflumethiazide 5–10 mg/day), amiloride (5–10 mg/day) and NSAIDs (e.g. indometacin 50 mg 3 times daily), although the last of these carries a risk of reducing glomerular filtration rate.

Disorders affecting multiple endocrine glands

Multiple endocrine neoplasia

Multiple endocrine neoplasias (MEN) are rare autosomal dominant syndromes characterised by hyperplasia, adenomas and/or malignant tumours in multiple glands. They fall into four groups, as shown in Box 20.60. Some other genetic diseases also have an increased risk of endocrine tumours; for example, phaeochromocytoma is associated with von Hippel–Lindau syndrome and neurofibromatosis type 1.

The MEN syndromes should be considered in all patients with two or more endocrine tumours and in patients with solitary tumours who report other endocrine tumours in their family. Inactivating mutations in *MEN1* (*MENIN*), a tumour suppressor gene on chromosome 11, cause MEN 1, whereas MEN 2a (also known as MEN 2) and 2b (also known as MEN 3) are caused by gain-of-function mutations in the *RET* proto-oncogene on chromosome 10. These cause constitutive activation of the membrane-associated tyrosine kinase RET, which controls the development of cells that migrate from the neural crest. In contrast, loss-of-function mutations of the RET kinase cause Hirschsprung disease. MEN 4 is extremely rare and is associated with loss-of-function mutations in the *CDNK1B* gene on chromosome 12; this gene codes for the protein p27, which has putative tumour suppressor activity. Predictive genetic testing can be performed on relatives of individuals with MEN syndromes, after appropriate counselling.

Individuals who carry pathogenic variants associated with MEN should be entered into a surveillance programme. In MEN 1, this typically involves annual history, examination and measurements of serum calcium and prolactin, and MRI of the pituitary and pancreas every 2 years; some centres also perform regular CT or MRI scans of the chest. In individuals with MEN 2a and 2b, annual history, examination and measurement of serum calcium, calcitonin and urinary or plasma catecholamine metabolites should be performed. Because the penetrance of medullary carcinoma of the thyroid approaches 100% in individuals with a *RET* pathogenic variant, prophylactic thyroidectomy should be performed in early childhood in most patients. The precise timing of surgery in childhood should be guided by the specific mutation in the *RET* gene.

i 20.60 Multiple endocrine neoplasia (MEN) syndromes

MEN 1 (Wermer syndrome)

- Primary hyperparathyroidism
- Pituitary tumours
- Pancreatic neuroendocrine tumours (e.g. non-functioning, insulinoma, gastrinoma)
- Bronchial and thymic carcinoids
- Adrenal tumours
- Cutaneous lesions (e.g. lipomas, collagenomas, angiofibromas)

MEN 2a (Sipple syndrome)

- Primary hyperparathyroidism
- Medullary carcinoma of thyroid
- Phaeochromocytoma

MEN 2b (also known as MEN 3)

- As for MEN 2a above (though medullary thyroid cancer occurs earlier, even within the first year of life)
- Marfanoid habitus
- Skeletal abnormalities (e.g. craniosynostosis)
- Abnormal dental enamel
- Multiple mucosal neuromas

MEN 4

- Primary hyperparathyroidism
- Pituitary tumours
- Possible tumours in the adrenals, reproductive organs, kidneys
- Possible pancreatic, gastric, bronchial and cervical neuroendocrine tumours

Autoimmune polyendocrine syndromes

Two distinct autoimmune polyendocrine syndromes are known: APS types 1 and 2.

The most common is APS type 2 (Schmidt syndrome), which typically presents in women between the ages of 20 and 60. It is usually defined as the occurrence in the same individual of two or more autoimmune endocrine disorders, some of which are listed in Box 20.61. The mode of inheritance is autosomal dominant with incomplete penetrance and there is a strong association with HLA-DR3 and CTLA-4.

Much less common is APS type 1, which is also termed autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED). This is inherited in an autosomal recessive fashion and is caused by loss-of-function mutations in the autoimmune regulator gene *AIRE*, which is responsible for the presentation of self-antigens to thymocytes in utero. This is essential for the deletion of thymocyte clones that react against self-antigens and hence for the development of immune tolerance. The most common clinical features are described in Box 20.61, although the pattern of presentation is variable and other autoimmune disorders are often observed.

Endocrine effects of cancer immunotherapy

Immune checkpoint inhibitors (ICIs) have transformed outcomes in highly aggressive cancers such as melanoma and lung cancer. The most common targets for these therapies are cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (e.g. ipilimumab) and programmed cell death protein 1 (PD-1) (e.g. nivolumab, pembrolizumab and cemiplimab). Hypophysitis occurs in up to 17% of people treated with ICI and

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20.61 Autoimmune polyendocrine syndromes (APS)*

Type 1 (APECED)

- Addison disease
- Hypoparathyroidism
- Type 1 diabetes
- Primary hypothyroidism
- Chronic mucocutaneous candidiasis
- Nail dystrophy
- Dental enamel hypoplasia

Type 2 (Schmidt syndrome)

- Addison disease
- Primary hypothyroidism
- Graves disease
- Pernicious anaemia
- Primary hypogonadism
- Type 1 diabetes
- Vitiligo
- Coeliac disease
- Myasthenia gravis

*In both types of APS, the precise pattern of disease varies between affected individuals.
(APECED = autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy)

is most likely to occur within the first six months of therapy. Thyroid dysfunction is most common within the first 8–12 weeks of therapy and is more likely in individuals treated with combination ICIs (up to 16%). Thyroid disease typically manifests as mild primary hypothyroidism, although transient thyrotoxicosis can precede this in some cases. Less commonly (~1%), patients may present with adrenalitis resulting in primary adrenal insufficiency or incident type 1 diabetes. It is suggested that glucose, TSH, free T4, morning cortisol (+/– ACTH), prolactin, gonadotrophins and oestradiol/testosterone are measured at baseline and every month for the first six months of ICI therapy. The development of ICI-related endocrinopathy should be investigated and treated but need not result in discontinuation of ICIs.

Further information

Websites

british-thyroid-association.org *British Thyroid Association: provider of guidelines, e.g. treatment of hypothyroidism and the investigation and management of thyroid cancer.*
btf-thyroid.org *British Thyroid Foundation: a resource for patient leaflets and support for patients with thyroid disorders.*
endocrinology.org *British Society for Endocrinology: useful online education resources and links to patient support group.*
endocrine.org *American Endocrine Society: provider of clinical practice guidelines.*
pituitary.org.uk *The Pituitary Foundation: a resource for patient and general practitioner leaflets and further information.*
thyroid.org *American Thyroid Association: provider of clinical practice guidelines.*

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Multiple Choice Questions

20.1. A 28-year-old man presents to his general practitioner with recent onset of weight loss, heat intolerance and palpitations. On examination a small goitre with a 2 cm discrete nodule is noted. Thyroid function tests show TSH < 0.01 mIU/L (RR 0.2–4.5 mIU/L), and free T4 25 pmol/L (RR 9–21 pmol/L. TSH receptor antibody (TRAb) is 1.1 IU/L (RR 0–1.6 IU/L). Prior to attendance at the endocrine clinic, a thyroid ultrasound is performed, which confirms a benign-looking 2 cm nodule in the context of a multinodular goitre. What would be the most appropriate next step?

A. Fine needle aspiration (FNA) of the nodule
B. Hemithyroidectomy
C. Carbimazole
D. Scintigraphy
E. Radio-iodine (400 MBq)

Answer: D.

The patient has thyrotoxicosis with an equivocal TRAb, no discriminatory clinical features of Graves disease and evidence of nodular thyroid disease. In this context, it is useful to perform scintigraphy to determine whether this is a 'hot' nodule (i.e. autonomously producing thyroid hormone). This has important implications, as 'hot' nodules are almost never malignant and treatment with radio-iodine has a high likelihood of restoring euthyroidism (as opposed to Graves disease, where the likeliest outcome is permanent hypothyroidism).

20.2. A 23-year-old recently married female presents to her family doctor with a 6-week history of 3 kg weight loss, an irregular menstrual cycle and anxiety. She has a fear of general anaesthesia due to a previous perioperative episode of anaphylaxis. She and her husband are keen to start a family. On examination a smooth goitre is palpable in her neck with bruit detected on auscultation. Thyroid function tests show TSH < 0.01 mIU/L (RR 0.2–4.5 mIU/L), and free T4 36 pmol/L (RR 9–21 pmol/L. TSH receptor antibody (TRAb) is 14 IU/L (RR 0–1.6 IU/L). What treatment for her thyrotoxicosis would you advise?

A. Carbimazole 20 mg once daily
B. 400 MBq radio-iodine
C. Subtotal thyroidectomy
D. Amiodarone 200 mg once daily
E. Propylthiouracil 100 mg twice daily

Answer: E.

The patient has clinical and biochemical evidence of Graves disease. Whilst carbimazole, radio-iodine and surgery are likely to be effective, they should be avoided in patients trying to conceive. Propylthiouracil has a lower risk of causing aplasia cutis in the developing embryo. An argument could be made for subtotal thyroidectomy to optimise thyroid status for conception, but her previous anaphylaxis shifts the risk–benefit in favour of medical management in the first instance. Amiodarone may make underlying thyrotoxicosis worse. Optimisation of thyroid status should be advised ahead of conception due to a higher risk of miscarriage, and a form of reliable contraception should be considered until she is euthyroid.

20.3. A 42-year-old male presented to his family doctor with a 6-month history of weight gain, fatigue and muscle weakness. The doctor noticed that he had centripetal obesity and abdominal striae and referred him to your endocrine clinic. The patient has no history of recent or current use of oral or inhaled steroids. You carry out some tests and find the following results:
Low-dose dexamethasone suppression test (LDDST): serum cortisol measured after 48 hours is 125 nmol/L (a normal response is a serum cortisol of < 50 nmol/L [1.8 µg/dL])
Late night (2300 hours) salivary cortisol: 18.4 nmol/L on the first occasion and 16.8 nmol/L on repeat testing (local RR < 3.6 nmol/L)
Plasma adrenocorticotrophic hormone (ACTH) at 0900 hours: undetectable (RR 1.5–13.9 pmol/L)

What would be the most appropriate next investigation to request in this patient?

A. Computed tomography (CT) of the adrenal glands
B. Corticotrophin-releasing hormone (CRH) stimulation test
C. High-dose dexamethasone suppression test (HDDST)
D. Magnetic resonance imaging (MRI) scan of the pituitary gland
E. Measurement of 24-hour urine free cortisol production

Answer: A.

The clinical features suggest Cushing syndrome, which is confirmed by the failure of cortisol suppression in the LDDST and the (repeated) high late-night cortisol level. The absence of detectable ACTH indicates an adrenal cause, with pituitary ACTH secretion being suppressed by high levels of cortisol. The most likely causes at this stage are a cortisol-secreting adrenal tumour (adenoma or, more rarely, carcinoma), so the most appropriate test is a CT scan of the adrenal glands.

There is no indication to carry out either a CRH stimulation test or an HDDST, as these tests are used to help to distinguish between pituitary-dependent Cushing syndrome and Cushing syndrome caused by ectopic ACTH secretion. Similarly, there is no indication for an MRI of the pituitary gland as the undetectable ACTH indicates an adrenal cause. 24-hour urine free cortisol production would be expected to be decreased, but this test is not necessary, as the diagnosis of Cushing syndrome has already been confirmed.

20.4. A 45-year-old man is incidentally found to have an elevated plasma calcium (2.7 mmol/L) on two separate occasions. Which of the following would make a diagnosis of familial hypocalciuric hypercalcaemia (FHH) more likely?

A. Normal plasma calcium recorded 5 years previously
B. PTH concentration within the reference range
C. Previous history of nephrolithiasis
D. Family history of hypercalcaemia in a first-degree relative
E. Previous history of osteoporosis

Answer: D.

FHH is an autosomal dominant condition caused by pathogenic variants in the calcium-sensing receptor (*CASR*) gene. It is typically associated with relatively modest hypercalcaemia and an absence of the end-organ damage associated with primary hyperparathyroidism. Previously normal calcium levels would be more consistent with the onset of primary hyperparathyroidism. PTH concentration in the upper half of the reference range is commonly encountered in primary hyperparathyroidism and does not help discriminate between this condition and FHH.

20.5. A 36-year-old man presents with frequent headaches and intermittent light-headedness and a single episode of syncope. On further questioning he notes some increased sweating and mentions there is a family history of hypercalcaemia in his mother and maternal aunt. His grandmother died suddenly at the age of 46 but the cause of death is not known. He is taking no medications. On assessment he is hypertensive with a blood

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pressure of 196/124 mmHg. He is clinically euthyroid and there are no discernable features of Cushing disease or acromegaly. Biochemical testing demonstrates TSH 2 mIU/L (RR 0.2–4.5 mIU/L), and free T4 14 pmol/L (RR 9–21 pmol/L); his corrected calcium is 2.72 mmol/L (RR 2.2–2.6 mmol/L); PTH is 7.2 pmol/L (RR 1.6–6.9 pmol/L). Plasma metanephrines are 2687 pmol/L (RR < 510 pmol/L). Testing of which gene is most likely to provide a definitive diagnosis?

A. *AIRE*
B. *RET*
C. *MENIN*
D. *VHL*
E. *CASR*

Answer: B.

The patient has symptoms and signs of phaeochromocytoma supported by raised plasma metanephrines. He also has asymptomatic hyperparathyroidism. The sudden death of his grandmother could have been the result of a hypertensive crisis. 40% of phaeochromocytomas are associated with pathogenic variants. Pathogenic variants in *AIRE* are associated with polyglandular autoimmunity and do not fit with this clinical picture. *CASR* pathogenic variants result in asymptomatic hypercalcaemia but are not associated with phaeochromocytoma. *MENIN* pathogenic variants are found in MEN 1, which is predominantly associated with pancreatic, parathyroid and pituitary lesions but not typically with phaeochromocytoma. Pathogenic variants in *VHL* increase the risk of phaeochromocytoma and haemangiomata but would not usually cause hyperparathyroidism. *RET* pathogenic variants are found in MEN 2a and MEN 2b. These conditions are typically associated with an increased risk of medullary thyroid carcinoma, phaeochromocytoma and primary hyperparathyroidism.